Petitions office

Attorney Docket No. 29,225 DAC.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 4,626,538

Granted: December 2, 1986

Title: [7-(3-Disubstituted Amino)phenyl]pyrazolo [1,5-a]pyrimidines

Assignee: American Cyanamid Company

Recorded: May 13, 1985 at Reel 4406/Frame 0769

BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Re: Deposit Account: 01-1300
U.S. Patent No. 4,626,538

Sir:

Transmitted herewith is an application for extension of patent term of U.S. Patent No. 4,626,538 in accordance with 35 USC 156 and a duplicate of the papers thereof, certified as such.

Please charge American Cyanamid Company Deposit Account No. 01-1300 in the amount of $1,120.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to American Cyanamid Company Account No. 01-1300. Two additional copies of this sheet are enclosed.

10/08/1999 SLUANG1 00000080 4626538
01 FC:111 1120.00 CH

Respectfully submitted,

Arnold S. Milowsky
Attorney for Applicants
Reg. No. 35,288

Dated: October 5, 1999
Telephone: (610) 902-2635

Attorney Docket No. 29,225

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Washington, D. C.. 20231

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 USC 156 including its attachments and supporting papers is a duplicate of the original application being currently submitted.

Arnold S. Milowsky
Attorney for Applicant
Reg. No. 35,288

Dated: 10/5/99

Telephone: (610) 902-2635

Attorney Docket No. 29,225

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 4,626,538

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Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING BY EXPRESS MAIL UNDER 37 CFR 1.10

"Express Mail" mailing label number: EL163890969US

Date of Deposit: October 5, 1999

I hereby certify that the following papers:

1. Letter of Transmittal of Application for Extension of Patent Term and Deposit Account charge order;

2. Application for Extension of Patent Term Under 35 USC 156 including Declaration and 5 Exhibits, plus duplicates of all papers, certified as such;

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to Box Patent Extension, Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Roxanne L. Kelly
(Typed or printed name of person mailing paper of fee)

Roxanne L. Kelly
(Signature of Person Mailing Paper or Fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,626,538

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BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, D. C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM
35 USC 156

Sir:

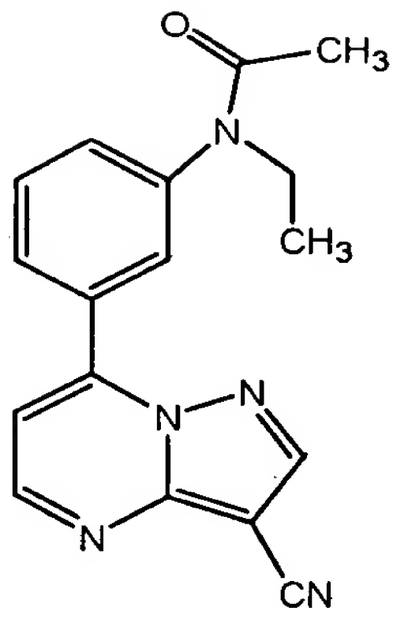
An extension of the patent term of U. S. Patent Number 4,626,538 is requested, based upon the following facts:

(1) The chemical name of the active ingredient of the approved product is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide.

The generic name of that compound is zaleplon.

The commercial name of the approved product is SONATA®.

The structural formula of zaleplon is:



The empirical formula for zaleplon is: $C_{17}H_{15}N_5O$.

The final draft of the Package Labeling for SONATA® (zaleplon) is attached as Exhibit I.

(2) The Federal statute including the applicable provision of law under which the regulatory review occurred is Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S. Sec. 301 et seq.

(3) The product received regulatory approval by the FDA on August 13, 1999 under the FFDCA, and received permission for commercial marketing on September 15, 1999, after receiving a Schedule IV classification under the Controlled Substances Act.

(4) The active ingredient in SONATA®, N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for submission pursuant to 35 USC §1.720(f), which sixty day period will expire October 12, 1999.

(6) The patent for which an extension is herewith being sought was granted to:

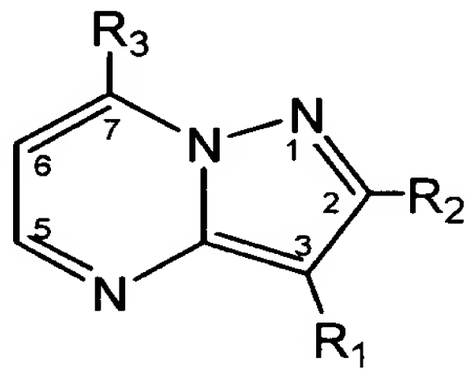
John P. Dusza, Andrew S. Tomcufcik, and Jay D. Albright as Patent Number 4,626,538 on December 2, 1986, which patent will expire June 23, 2003. The term of the patent has not previously been extended.

(7) A copy of the patent for which this extension is sought is attached as Exhibit II. No other patent term has been extended for the same regulatory review period for SONATA® (zaleplon).

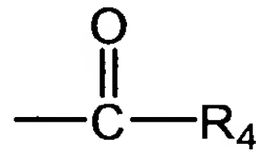
(8) A copy of the maintenance fee payments made for US Patent Number 4,626,538 are attached as Exhibit III. A copy of the Terminal Disclaimer, Request for Certificate of Correction, and Decision Granting Petition for Certificate of Correction is attached as Exhibit IV.

(9) Claims 1, 2, 4, 14, and 15 of US Patent Number 4,626,538 claim the approved product. As follows, the claims are underlined in a manner showing the relevant claim portions covering the active ingredient of SONATA®.

Claim 1. A compound of the formula



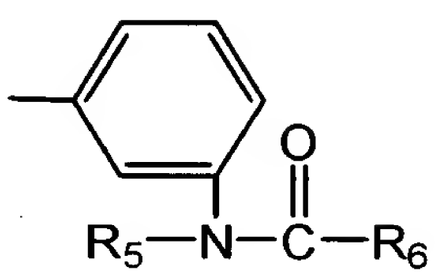
wherein R_1 is selected from the group consisting of hydrogen, halogen, cyano and



;

R_2 is selected from the group consisting of hydrogen and alkyl (C_1-C_3);

R_3 is

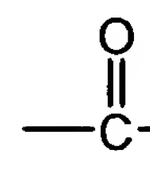


R_4 is selected from the group consisting of hydrogen, alkyl (C_1-C_6) and alkoxy (C_1-C_6);

R_5 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), $-CH_2C{\equiv}CH$, cycloalkyl(C_3-C_6)methyl, $-CH_2OCH_3$ and $-CH_2CH_2OCH_3$; and

R6 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_3), -N-dialkyl(C_1-C_3), $-(CH_2)_n$-O-alkyl(C_1-C_3), $-(CH_2)_n$-NH-alkyl(C_1-C_3) and $-(CH_2)_n$-N-dialkyl(C_1-C_3), where n is an integer 1 to 3 inclusive.

Claim 2. A compound according to claim **1**, wherein R_1 is cyano or



R_2 is hydrogen;

R_4 is alkyl(C_1-C_6), alkenyl(C_2-C_6) or $-CH_2{\equiv}CH$; and

R_6 is alkyl(C_1-C_6), cycloalkyl(C_3-C_6) or -O-alkyl(C_1-C_6).

Claim 4. The compound according to claim **2**, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide.

Claim 14. A method of ameliorating anxiety in a mammal which comprises administering to said mammal an amount of a compound of claim **1** sufficient to reduce anxiety.

Claim 15. A composition of matter in dosage unit form comprising from 2-750 mg of a command of claim **1** in association with a pharmaceutically acceptable carrier.

(10) The dates and information necessary for the Secretary of HHS to determine the applicable regulatory review period under 35 USC 156(g) can be determined from the following facts:

a) The Investigational New Drug Application (IND) for zaleplon hydrochloride was submitted to the Food and Drug Agency (FDA) on April 16, 1991.

b) Receipt of the IND by the FDA on April 16, 1991, was acknowledged on April 24, 1991 and IND number 36,751 was assigned the application. Hence the effective date for IND 36,751 is May 16, 1991, 30 days after receipt of the IND.

c) The New Drug Application (NDA) for zaleplon was submitted to the FDA on December 30, 1997, and received by the FDA on January 6, 1998.

d) Receipt of the NDA by the FDA was acknowledged on January 13, 1998 and NDA number 20-859 was assigned the application.

e) The NDA for SONATA® (zaleplon) was approved on August 13, 1999. SONATA® (zaleplon) could not be commercially marketed on August 13, 1999 as it was required to undergo review under the Controlled Substances Act by the Drug Enforcement Administration (DEA) to determine DEA Schedule classification. Such review cannot occur before NDA approval.

f) SONATA® (zaleplon) received DEA Schedule IV classification under the Controlled Substances Act, and was first eligible for commercial marketing on September 15, 1999.

(11) To briefly describe applicant's activities with respect to zaleplon during the applicable regulatory review period, Exhibit V is attached, to provide an abbreviated list of the most significant correspondence with the FDA and activities undertaken from April 16, 1991 to the present time.

(12) It is Applicant's opinion that US Patent Number 4,626,538 is eligible for an extension of a period of 5 years, based upon the following calculation:

a) One half of the IND time from May 16, 1991 to December 29, 1997 (6 years, 7 months, 16 days) is 3 years, 3 months, 25 days (1210 days).

b) All the NDA time from December 30, 1997 to approval on August 13, 1999 (592 days) plus all time under DEA scheduling review from August 13, 1999 to September 15, 1999 (33 days) is 1 years, 8 months, 17 days (625 days).

c) Total: 5 years, 0 months, 10 days (1835 days).

Hence, under 35 USC 156(g)(6)(A), the patent is entitled to a 5 year extension period.

(13) Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The $1,120 fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account as authorized in the attached transmittal letter, which is submitted in triplicate.

(15) Inquiries relating to this application for patent term extension may be directed to Arnold S. Milowsky, at telephone number (610) 902-2635. All written correspondence should be addressed to Egon Berg, American Home Products Corporation, One Campus Drive, Parsippany, New Jersey, 07054.

(16) A certified duplicate of these application papers accompanies this application.

(17) The required oath is attached hereto.

Respectfully submitted,

Arnold S. Milowsky
Attorney for Applicant
Reg. No. 35,288

Dated: 10/4/99

Telephone: (610) 902-2635

Attorney Docket No. 29,225

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BOX PATENT EXTENSION
Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER RULE 740(a)(17)

Sir:

I, Arnold S. Milowsky, am a Patent Attorney registered to practice before the US Patent and Trademark Office, presently employed by American Home Products Corporation, with authority to act for American Cyanamid Company in this Application for Extension of Patent Term under 35 USC 156; state:

(1) THAT, I have reviewed and understand the contents of the application being submitted pursuant to 35 USC 156, and 37 CFR 1.710;

(2) THAT, I believe the patent is subject to extension pursuant to 37 CFR 1.710;

(3) THAT, I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations;

(4) THAT, I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 CFR 1.720;

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

FURTHER, declarant sayeth not.

Date: 10/4/99

Arnold S. Milowsky
Attorney for Applicant
Reg. No. 35,288

Exhibit I

Final Package Labeling for SONATA® (zaleplon)

13-AUG-99

FINAL LABELING

Sonata
(Zaleplon)

DESCRIPTION

Zaleplon is a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class. The chemical name of zaleplon is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide. Its empirical formula is $C_{17}H_{15}N_5O$, and its molecular weight is 305.34. The structural formula is shown below.

[Structure here.]

Zaleplon is a white to off-white powder that is practically insoluble in water and sparingly soluble in alcohol or propylene glycol. Its partition coefficient in octanol/water is constant (log PC = 1.23) over the pH range of 1 to 7.

Sonata® capsules contain zaleplon as the active ingredient. Inactive ingredients consist of microcrystalline cellulose, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, magnesium stearate, lactose, gelatin, titanium dioxide, D&C yellow #10, FD&C blue #1, FD&C green #3, and FD&C yellow #5.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

While Sonata (zaleplon) is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with the GABA-BZ receptor complex. Subunit modulation of the GABA-BZ receptor chloride channel macromolecular complex is hypothesized to be responsible for some of the pharmacological properties of benzodiazepines, which include sedative, anxiolytic, muscle relaxant, and anticonvulsive effects in animal models.

Other nonclinical studies have also shown that zaleplon binds selectively to the brain omega-1 receptor situated on the alpha subunit of the $GABA_A$ receptor complex and potentiates t-butyl-bicyclophosphorothionate (TBPS) binding. Studies of binding of zaleplon to purified $GABA_A$ receptors ($\alpha1\beta1\gamma2$ [omega-1] and $\alpha2\beta1\gamma2$ [omega-2]) have shown that zaleplon has a low affinity for these receptors, with preferential binding to the omega-1 receptor.

Pharmacokinetics

The pharmacokinetics of zaleplon have been investigated in more than 500 healthy subjects (young and elderly), nursing mothers, and patients with hepatic disease or renal disease. In healthy subjects, the pharmacokinetic profile has been examined after single doses of up to 60 mg and once-daily administration at 15 and 30 mg for 10 days. Zaleplon was rapidly absorbed with a time to peak concentration (tmax) of approximately 1 hour and a terminal-phase elimination half-life (t1/2) of approximately 1 hour. Zaleplon does not accumulate with once-daily administration and its pharmacokinetics are dose proportional in the therapeutic range.

Absorption

Zaleplon is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are attained within approximately 1 hour after oral administration. Although zaleplon is well absorbed, its absolute bioavailability is approximately 30% because it undergoes significant presystemic metabolism.

Distribution

Zaleplon is a lipophilic compound with a volume of distribution of approximately 1.4 L/kg following intravenous (iv) administration, indicating substantial distribution into extravascular tissues. The in vitro plasma protein binding is approximately 60% ±15% and is independent of zaleplon concentration over the range of 10 to 1000 ng/mL. This suggests that zaleplon disposition should not be sensitive to alterations in protein binding. The blood to plasma ratio for zaleplon is approximately 1, indicating that zaleplon is uniformly distributed throughout the blood with no extensive distribution into red blood cells.

Metabolism

After oral administration, zaleplon is extensively metabolized, with less than 1% of the dose excreted unchanged in urine. Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. Zaleplon is metabolized to a lesser extent by CYP3A4 to form desethylzaleplon, which is quickly converted, presumably by aldehyde oxidase, to 5-oxo-desethylzaleplon. These oxidative metabolites are then converted to glucuronides and eliminated in urine. All of zaleplon's metabolites are pharmacologically inactive.

Elimination

After either oral or iv administration, zaleplon is rapidly eliminated with mean t½ of approximately 1 hour. The oral-dose plasma clearance of zaleplon is about 3 L/h/kg and the iv zaleplon plasma clearance is approximately 1 L/h/kg. Assuming normal hepatic blood flow and negligible renal clearance of zaleplon, the estimated hepatic extraction ratio of zaleplon is approximately 0.7, indicating that zaleplon is subject to high first-pass metabolism.

After administration of a radiolabeled dose of zaleplon, 70% of the administered dose is recovered in urine within 48 hours (71% recovered within 6 days), almost all as zaleplon metabolites and their glucorinides. An additional 17% is recovered in feces within 6 days, most as 5-oxo-zaleplon.

Effect of Food

In healthy adults a high fat/heavy meal prolonged the absorption of zaleplon compared to the fasted state, delaying tmax by approximately 2 hours and reducing Cmax by approximately 35%. Zaleplon AUC and elimination half-life were not significantly affected. These results suggest that the effects of Sonata on sleep onset may be reduced if it is taken with or immediately after a high-fat, heavy meal.

Special Populations

Age - The pharmacokinetics of Sonata have been investigated in three studies with elderly men and women ranging in age from 65 to 85 years. The pharmacokinetics of Sonata in elderly subjects, including those over 75 years of age, are not significantly different from those in young healthy subjects.

Gender - There is no significant difference in the pharmacokinetics of Sonata in men and women.

Race - The pharmacokinetics of zaleplon have been studied in Japanese subjects as representative of Asian populations. For this group, Cmax and AUC were increased 37% and 64%, respectively. This finding can likely be attributed to differences in body weight, or alternatively, may represent differences in enzyme activities resulting from differences in diet, environment, or other factors. The effects of race on pharmacokinetic characteristics in other ethnic groups have not been well characterized.

Hepatic impairment - Zaleplon is metabolized primarily by the liver and undergoes significant presystemic metabolism. Consequently, the oral clearance of zaleplon was reduced by 70% and 87% in compensated and decompensated cirrhotic patients, respectively, leading to marked increases in mean Cmax and AUC (up to 4-fold and 7- fold in compensated and decompensated patients, respectively), in comparison with healthy subjects. The dose of Sonata should therefore be reduced in patients with mild to moderate hepatic impairment (See **DOSAGE AND ADMINISTRATION**). Sonata is not recommended for use in patients with severe hepatic impairment.

Renal impairment - Because renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose, the pharmacokinetics of zaleplon are not altered in patients with renal insufficiency. No dose adjustment is necessary in patients with mild to moderate renal impairment. Sonata has not been adequately studied in patients with severe renal impairment.

Drug-Drug Interactions

Because zaleplon is primarily metabolized by aldehyde oxidase, and to a lesser extent by CYP3A4, inhibitors of these enzymes might be expected to decrease zaleplon's clearance and inducers of these enzymes might be expected to increase its clearance. Zaleplon has been shown to have minimal effects on the kinetics of warfarin (both R- and S- forms), imipramine, ethanol, ibuprofen, diphenhydramine, thioridazine, and digoxin. However, the effects of zaleplon on inhibition of enzymes involved in the metabolism of other drugs has not been studied (See Drug Interactions under Precautions).

Clinical Trials

Controlled Trials Supporting Effectiveness

Sonata (typically administered in doses of 5, 10, or 20 mg) has been studied in patients with chronic insomnia (n = 3298) in 11 placebo and active controlled trials. Three of the trials were in elderly patients (n = 1019). It has also been studied in transient insomnia (n=264). Because of its very short half-life, studies focused on decreasing sleep latency, with less attention to duration of sleep and number of awakenings, for which consistent differences from placebo were not demonstrated. Studies were also carried out to examine the time course of effects on memory and psychomotor function, and to examine withdrawal phenomena.

Transient Insomnia

Normal adults experiencing transient insomnia during the first night in a sleep laboratory were evaluated in a double-blind, parallel-group trial comparing the effects of two doses of Sonata (5 and 10 mg) with placebo. Sonata 10 mg, but not 5 mg, was superior to placebo in decreasing latency to persistent sleep (LPS), a polysomnographic measure of time to onset of sleep.

Chronic Insomnia

Non-Elderly Patients:

Adult outpatients with chronic insomnia were evaluated in three double-blind, parallel-group outpatient studies, one of 2-weeks duration and two of 4-weeks duration, that compared the effects of Sonata at doses of 5 (in two studies), 10, and 20 mg with placebo on a subjective measure of time to sleep onset (TSO). Sonata 10 and 20 mg were consistently superior to placebo for TSO, generally for the full duration of all three studies. Although both doses were effective, the effect was greater and more consistent for the 20-mg dose. The 5-mg dose was less consistently effective than were the 10- and 20-mg doses. Sleep latency with Sonata 10 and 20 mg was on the order of 10-20 minutes (15%-30%) less than with placebo in these studies.

Adult outpatients with chronic insomnia were evaluated in five double-blind, parallel-group sleep laboratory studies that varied in duration from a single night up to 28 days. Overall, these studies demonstrated a superiority of Sonata 10 and 20 mg over placebo in reducing latency to persistent sleep (LPS) on the first 2 nights of treatment. A reduction in LPS relative to baseline was observed for all treatment groups, including placebo, at later time points, and, thus, a significant difference from placebo was not seen beyond 2 nights.

Elderly Patients:

Elderly outpatients with chronic insomnia were evaluated in two 2-week, double-blind, parallel-group outpatient studies that compared the effects of Sonata 5 and 10 mg with placebo on a subjective measure of time to sleep onset (TSO). Sonata at both doses was superior to placebo on TSO, generally for the full duration of both studies, with an effect size generally similar to that seen in younger persons. The 10-mg dose tended to have a greater effect in reducing TSO.

Elderly outpatients with chronic insomnia were also evaluated in a 2-night sleep laboratory study involving doses of 5 and 10 mg. Both 5- and 10-mg doses of Sonata were superior to placebo in reducing latency to persistent sleep (LPS).

Generally in these studies there was a slight increase in sleep duration, compared to baseline, for all treatment groups, including placebo, and thus, a significant difference from placebo on sleep duration was not demonstrated.

<u>Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs</u>

Memory Impairment

Studies involving the exposure of normal subjects to single fixed doses of Sonata (10 or 20 mg) with structured assessments of short-term memory at fixed times after dosing (e.g., 1, 2, 3, 4, 5, 8, and 10 hours) generally revealed the expected impairment of short-term memory at 1 hour, the time of peak exposure to zaleplon, for both doses, with a tendency for the effect to be greater after 20 mg. Consistent with the rapid clearance of zaleplon, memory impairment was no longer present as early as 2 hours post dosing in one study, and in none of the studies after 3-4 hours. Nevertheless, spontaneous reporting of adverse events in larger premarketing clinical trials revealed a difference between Sonata and placebo in the risk of next-day amnesia (3% vs 1%), and an apparent dose-dependency for this event (see Adverse Reactions).

Sedative/Psychomotor Effects

Studies involving the exposure of normal subjects to single fixed doses of Sonata (10 or 20 mg) with structured assessments of sedation and psychomotor function (e.g., reaction time and subjective ratings of alertness) at fixed times after dosing (e.g., 1, 2, 3, 4, 5, 8, and 10 hours) generally revealed the expected sedation and impairment of psychomotor function at 1 hour, the time of peak exposure to zaleplon, for both doses. Consistent with the rapid clearance of zaleplon, impairment of psychomotor function was no longer present as early as 2 hours post dosing in one study, and in none of the studies after 3-4 hours. Spontaneous reporting of adverse events in larger premarketing clinical trials did not suggest a difference between Sonata and placebo in the risk of next-day somnolence (see Adverse Reactions).

Withdrawal Emergent Anxiety and Insomnia

During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events is believed to be responsible for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics: increased wakefulness during the last quarter of the night and the appearance of increased signs of daytime anxiety.

Zaleplon has a short half-life and no active metabolites. There is insufficient evidence to assess whether or not Sonata use is associated with increased wakefulness during the latter part of the night. No increase in the signs of daytime anxiety were observed in clinical trials with Sonata. In two sleep laboratory studies involving 14 and 28 days of nightly Sonata dosing (5 and 10 mg in one study and 10 and 20 mg in the second) and structured assessments of daytime anxiety, no increases in daytime anxiety were detected. Similarly, in a pooled analysis (all the parallel group, placebo controlled studies) of spontaneously reported daytime anxiety, no difference was observed between Sonata and placebo.

Rebound insomnia, defined as a dose-dependent temporary worsening in sleep parameters (latency, total sleep time, and number of awakenings) following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. Rebound insomnia following discontinuation of Sonata relative to baseline was examined at both nights 1 and 2 following discontinuation in two sleep laboratory studies (14 and 28 nights) and five outpatient studies utilizing patient diaries (14 and 28 nights). Overall, the data suggest that rebound insomnia may be dose dependent. At 20 mg, there appeared to be both objective (PSG) and subjective (diary) evidence of rebound insomnia on the first night after discontinuation of treatment with Sonata. At 5 and 10 mg, there was no objective and minimal subjective evidence of rebound insomnia on the first night after discontinuation of treatment with Sonata. At all doses, the rebound effect appeared to resolve by the second night following withdrawal.

Other Withdrawal-Emergent Phenomena

The potential for other withdrawal phenomena was also assessed for in 14 to 28 day studies, including both the sleep laboratory studies and the outpatient studies, and in open-label studies of 6- and 12-month durations. The Benzodiazepine Withdrawal Symptom Questionnaire was used in several of these studies, both at baseline and then during days 1 and 2 following discontinuation. Withdrawal was operationally defined as the emergence of 3 or more new symptoms after discontinuation. Sonata was not distinguishable from placebo at doses of 5, 10, or 20 mg on this measure, nor was Sonata distinguishable from placebo on spontaneously reported withdrawal emergent adverse events. There were no instances of withdrawal delirium, withdrawal associated hallucinations, or any other manifestations of severe sedative/hypnotic withdrawal.

INDICATIONS AND USAGE

Sonata is indicated for the short-term treatment of insomnia. Sonata has been shown to decrease the time to sleep onset for up to 28 days in controlled clinical studies (see Clinical Trials under Clinical Pharmacology). It has not been shown to increase total sleep time or decrease the number of awakenings.

Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Sonata should not be prescribed in quantities exceeding a 1-month supply (see WARNINGS).

CONTRAINDICATIONS

None known.

WARNINGS

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Sonata. Because some of the important adverse effects of Sonata appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see DOSAGE AND ADMINISTRATION).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

Sonata, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, Sonata should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving Sonata should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Sonata. Sonata, as well as other hypnotics, may produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. Sonata should not be taken with alcohol. Dosage adjustment may be necessary when Sonata is administered with other CNS depressant agents because of the potentially additive effects.

PRECAUTIONS

General

Timing of Drug Administration

Sonata should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep. As with all sedative/hypnotics, taking Sonata while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use in the elderly and/or debilitated patients

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. A dose of 5 mg is recommended for elderly patients to decrease the possibility of side effects (see DOSAGE AND ADMINISTRATION). Elderly and/or debilitated patients should be monitored closely.

Use in patients with concomitant illness

Clinical experience with Sonata in patients with concomitant systemic illness is limited. Sonata should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of Sonata in normal subjects, caution should be observed if Sonata is prescribed to patients with compromised respiratory function, because sedative/hypnotics have the capacity to depress respiratory drive. Controlled trials of acute administration of Sonata 10 mg in patients with chronic obstructive pulmonary disease or moderate obstructive sleep apnea showed no evidence of alterations in blood gases or apnea/hypopnea index, respectively. However, patients with compromised respiration due to preexisting illness should be monitored carefully.

The dose of Sonata should be reduced to 5 mg in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). It is not recommended for use in patients with severe hepatic impairment.

No dose adjustment is necessary in patients with mild to moderate renal impairment. Sonata has not been adequately studied in patients with severe renal impairment.

Use in patients with depression

As with other sedative/hypnotic drugs, Sonata should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients (see OVERDOSAGE); therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for Patients

Patient information is printed at the end of this insert. To assure safe and effective use of Sonata, the information and instructions provided in the patient information section should be discussed with patients.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential exists for interaction with other drugs by a variety of mechanisms.

CNS-active Drugs

Ethanol - Sonata 10 mg potentiated the CNS-impairing effects of ethanol 0.75 g/kg on balance testing and reaction time for 1 hour after ethanol administration and on the digit symbol substitution test (DSST), symbol copying test, and the variability component of the divided attention test for 2.5 hours after ethanol administration. The potentiation resulted from a CNS pharmacodynamic interaction; zaleplon did not affect the pharmacokinetics of ethanol.

Imipramine - Coadministration of single doses of Sonata 20 mg and imipramine 75 mg produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration. The interaction was pharmacodynamic with no alteration of the pharmacokinetics of either drug.

Paroxetine - Coadministration of a single dose of Sonata 20 mg and paroxetine 20 mg daily for 7 days did not produce any interaction on psychomotor performance. Additionally, paroxetine did not alter the pharmacokinetics of Sonata, reflecting the absence of a role of CYP2D6 in zaleplon's metabolism.

Thioridazine - Coadministration of single doses of Sonata 20 mg and thioridazine 50 mg produced additive effects of decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration. The interaction was pharmacodynamic with no alteration of the pharmacokinetics of either drug.

Drugs that Induce CYP3A4

Rifampin - CYP3A4 is ordinarily a minor metabolizing enzyme of zaleplon. Multiple-dose administration of the potent CYP3A4 inducer rifampin (600 mg every 24 hours, q24h, for 14 days), however, reduced zaleplon Cmax and AUC by approximately 80%. The coadministration of a potent CYP3A4 enzyme inducer, although not posing a safety concern, thus could lead to ineffectiveness of zaleplon. An alternative non-CYP3A4 substrate hypnotic agent may be considered in patients taking CYP3A4 inducers such as rifampin, phenytoin, carbamazapine and phenobarbital.

Drugs that Inhibit CYP3A4

CYP3A4 is a minor metabolic pathway for the elimination of zaleplon because the sum of desethylzaleplon (formed via CYP3A4 in vitro) and its metabolites, 5-oxo-desethylzaleplon and 5-oxo-desethylzaleplon glucuronide, account for only 9% of the urinary recovery of a zaleplon dose. The coadministration of a potent, selective CYP3A4 inhibitor is therefore not expected to produce a clinically important pharmacokinetic interaction with zaleplon; however, there are no clinical studies specifically addressing this question.

Drugs that Inhibit Aldehyde Oxidase

The aldehyde oxidase enzyme system is less well studied than the cytochrome P450 enzyme system.

Diphenhydramine - Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver, but its inhibitory effects in human liver are not known. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50 mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible.

Drugs that Inhibit Both Aldehyde Oxidase and CYP3A4

Cimetidine - Cimetidine inhibits both aldehyde oxidase (in vitro) and CYP3A4 (in vitro and in vivo), the primary and secondary enzymes, respectively, responsible for zaleplon metabolism. Concomitant administration of Sonata (10 mg) and cimetidine (800 mg) produced an 85% increase in the mean Cmax and AUC of zaleplon. An initial dose of 5 mg should be given to patients who are concomitantly being treated with cimetidine **(SEE DOSAGE AND ADMINISTRATION).**

Drugs Highly Bound to Plasma Protein

Zaleplon is not highly bound to plasma proteins (fraction bound 60%±15%); therefore, the disposition of zaleplon is not expected to be sensitive to alterations in protein binding. In addition, administration of Sonata to a patient taking another drug that is highly protein bound should not cause transient increase in free concentrations of the other drug.

Drugs with a Narrow Therapeutic Index

Digoxin - Sonata (10 mg) did not affect the pharmacokinetic or pharmacodynamic profile of digoxin (0.375 mg q24h for 8 days).

Warfarin - Multiple oral doses of Sonata (20 mg q24h for 13 days) did not affect the pharmacokinetics of warfarin (R+)- or (S-)-enantiomers or the pharmacodynamics (prothrombin time) following a single 25 mg oral dose of warfarin.

Drugs that Alter Renal Excretion

Ibuprofen - Ibuprofen is known to affect renal function and, consequently, alter the renal excretion of other drugs. There was no apparent pharmacokinetic interaction between zaleplon and ibuprofen following single dose administration (10 mg and 600 mg, respectively) of each drug. This was expected because zaleplon is primarily metabolized and renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies of zaleplon were conducted in mice and rats. Mice received doses of 25, 50, 100, and 200mg/kg/day in the diet for two years. These doses are equivalent to 6-49 times the maximum recommended human dose (MHRD) of 20 mg on a mg/m^2 basis. There was a significant increase in the incidence of hepatocellular adenomas in female mice in the high dose group. Rats received doses of 1, 10, and 20mg/kg/day in the diet for two years. These doses are equivalent to 0.5-10 times the maximum recommended human dose (MHRD) of 20 mg on a mg/m^2 basis. Zaleplon was not carcinogenic in rats.

Mutagenesis

Zaleplon was clastogenic, both in the presence and absence of metabolic activation, causing structural and numerical aberrations (polyploidy and endoreduplication), when tested for chromosomal aberrations in the *in vitro* Chinese hamster ovary cell assay. In the *in vitro* human lymphocyte assay, zaleplon caused numerical but not structural aberrations, only in the presence of metabolic activation at the highest concentrations tested. In other *in vitro* assays, zaleplon was not mutagenic in the Ames bacterial gene mutation assay or the Chinese hamster ovary HGPRT gene mutation assay. Zaleplon was not clastogenic in two *in vivo* assays, the mouse bone marrow micronucleus assay and the rat bone marrow chromosomal aberration assay, and did not cause DNA damage in the rat hepatocyte unscheduled DNA synthesis assay.

Impairment of Fertility

In a fertility and reproductive performance study in rats, mortality and decreased fertility were associated with administration of an oral dose of zaleplon of 100 mg/kg/day to males and females prior to and during mating. This dose is equivalent to 49 times the maximum recommended human dose (MHRD) of 20 mg on a mg/m^2 basis. Follow-up studies indicated that impaired fertility was due to an effect on the female.

Pregnancy: Pregnancy Category C:

In embryofetal development studies in rats and rabbits, oral administration of up to 100 and 50 mg/kg/day, respectively, to pregnant animals throughout organogenesis produced no evidence of teratogenicity. These doses are equivalent to 49 (rat) and 48 (rabbit) times the maximum recommended human dose (MHRD) of 20 mg on a mg/m^2 basis. In rats, pre- and postnatal growth was reduced in the offspring of dams receiving 100 mg/kg/day. This dose was also maternally toxic, as evidenced by clinical signs and decreased maternal body weight gain during gestation. The no effect dose for rat offspring growth reduction was 10 mg/kg (a dose equivalent to 5 times the MHRD of 20 mg on a mg/m^2 basis). No adverse effects on embryofetal development were observed in rabbits at the doses examined.

In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of 7 mg/kg/day or greater during the latter part of gestation and throughout lactation. There was no evidence of maternal toxicity at this dose. The no-effect dose for offspring development was 1 mg/kg/day (a dose equivalent to 0.5 times the MHRD of 20 mg on a mg/m^2 basis). When the adverse effects on offspring viability and growth were examined in a cross-fostering study, they appeared to result from both *in utero* and lactational exposure to the drug.

There are no studies of zaleplon in pregnant women; therefore, Sonata is not recommended for use in women during pregnancy.

Labor and Delivery

Sonata has no established use in labor and delivery.

Nursing Mothers

A study in lactating mothers indicated that the clearance and half-life of zaleplon is similar to that in young normal subjects. A small amount of zaleplon is excreted in breast milk, with the highest excreted amount occurring during a feeding at approximately 1 hour after Sonata administration. Since the small amount of the drug from breast milk may result in potentially important concentrations in infants, and because the effects of zaleplon on a nursing infant are not known, it is recommended that nursing mothers not take Sonata.

Pediatric Use

The safety and effectiveness of Sonata in pediatric patients have not been established.

Geriatric Use

A total of 628 patients in double-blind, placebo-controlled, parallel-group clinical trials who received Sonata were at least 65 years of age; of these 311 received 5 mg and 317 received 10 mg. In both sleep laboratory and outpatient studies elderly patients with insomnia responded to a 5 mg dose with a reduced sleep latency, and thus 5 mg is the recommended dose in this population. During short-term treatment (14 night studies) of elderly patients with Sonata, no adverse event with a frequency of at least 1% occurred at a significantly higher rate with either 5 mg or 10 mg Sonata than with placebo.

ADVERSE REACTIONS

The premarketing development program for Sonata included zaleplon exposures in patients and/or normal subjects from 2 different groups of studies: approximately 900 normal subjects in clinical pharmacology/pharmacokinetic studies; and approximately 2800 exposures from patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 450 patient exposure years. The conditions and duration of treatment with Sonata varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

<u>Adverse Events Associated with Discontinuation of Treatment</u>

In premarketing placebo-controlled, parallel-group phase 2-3 clinical trials, 3.1% of 744 patients who received placebo and 3.5% of 2,069 patients who received Sonata discontinued treatment because of an adverse clinical event. This difference was not statistically significant. No event that resulted in discontinuation occurred at a rate of $\geq$ 1%.

Adverse Events Occurring at an Incidence of 1% or more Among Sonata 20 mg-Treated Patients

Table 1 enumerates, for a pool of three placebo-controlled 28-night studies of Sonata at doses of 5 or 10 mg and 20 mg, the incidence of treatment emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with Sonata 20 mg where the incidence in patients treated with Sonata 20 mg was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1

Incidence (%) of Treatment-Emergent Events in Long-Term (28 Nights) Placebo-Controlled Clinical Trials of Sonata

Body system Preferred Term	Placebo (n=277)	Sonata 5 or 10 mg (n=513)	Sonata 20 mg (n=273)
~~Body~~ as a whole			
Abdominal pain	4	5	6
Asthenia	5	5	8
Fever	1	2	2
Headache	31	28	38
Malaise	<1	<1	2
Photosensitivity Reaction	<1	<1	1
Digestive system			
Anorexia	<1	<1	2
Colitis	0	0	1
Dyspepsia	5	4	7
Nausea	7	7	8
Metabolic and nutritional			
Peripheral edema	<1	<1	1
Musculoskeletal system			
Myalgia	4	7	5
Nervous system			
Amnesia	1	2	4
Anxiety	2	<1	3
Depersonalization	<1	<1	2
Dizziness	7	7	8
Hallucinations	<1	<1	1
Hypesthesia	0	<1	2
Paresthesia	1	3	3
Somnolence	3	5	5
Tremor	1	2	2
Vertigo	<1	<1	1
Respiratory system			
Epistaxis	0	<1	1
Special senses			
Abnormal vision	<1	<1	2
Ear pain	0	<1	1
Eye pain	3	4	4
Hyperacusis	<1	2	2
Parosmia	1	<1	2

Urogenital system			
Dysmenorrhea	2	2	4

[1]:Events for which the incidence for Sonata 20 mg-treated patients was at least1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

Other Events Observed During the Premarketing Evaluation of Sonata

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with Sonata at doses in a range of 5 to 20 mg/day during premarketing phase 2 and 3 clinical trials throughout the United States, Canada, and Europe including approximately 2800 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, and those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with Sonata, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a whole - Frequent: back pain, chest pain; Infrequent: chest pain substernal, chills, face edema, generalized edema, hangover effect, neck rigidity.

Cardiovascular system – Frequent: migraine; Infrequent: angina pectoris, bundle branch block, hypertension, hypotension, palpitation, syncope, tachycardia, vasodilatation, ventricular extrasystoles; Rare: bigeminy, cerebral ischemia, cyanosis, pericardial effusion, postural hypotension, pulmonary embolus, sinus bradycardia, thrombophlebitis, ventricular tachycardia.

Digestive system - Frequent: constipation, dry mouth; Infrequent: eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, increased appetite, melena, mouth ulceration, rectal hemorrhage, stomatitis; Rare: aphthous stomatitis, biliary pain, bruxism, cardiospasm, cheilitis, cholelithiasis, duodenal ulcer, dysphagia, enteritis, gum hemorrhage, increased salivation, intestinal obstruction, liver function tests abnormal, peptic ulcer, tongue discoloration, tongue edema, ulcerative stomatitis.

Endocrine system - Rare: diabetes mellitus, goiter, hypothyroidism.

Hemic and lymphatic system - Infrequent: anemia, ecchymosis, lymphadenopathy; Rare: eosinophilia, leukocytosis, lymphocytosis, purpura.

Metabolic and nutritional - Infrequent: edema, gout, hypercholesteremia, thirst, weight gain; Rare: bilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoglycemic reaction, ketosis, SGOT increased, SGPT increased, weight loss.

Musculoskeletal system - Frequent: arthritis; Infrequent: arthrosis, bursitis, joint disorder (mainly swelling, stiffness, and pain), myasthenia, tenosynovitis; Rare: myositis, osteoporosis.

Nervous system – Frequent: depression, hypertonia, nervousness, thinking abnormal (mainly difficulty concentrating); Infrequent: abnormal gait, agitation, apathy, ataxia, circumoral paresthesia, confusion, emotional lability, euphoria, hyperesthesia, hyperkinesia, hypotonia, incoordination, insomnia, libido decreased, neuralgia, nystagmus; Rare: CNS stimulation, delusions, dysarthria, dystonia, facial paralysis, hostility, hypokinesia, myoclonus, neuropathy, psychomotor retardation, ptosis, reflexes decreased, reflexes increased, sleep talking, sleep walking, slurred speech, stupor, trismus.

Respiratory system - Frequent: bronchitis; Infrequent: asthma, dyspnea, laryngitis, pneumonia, snoring, voice alteration; Rare: apnea, hiccup, hyperventilation, pleural effusion, sputum increased.

Skin and appendages - Frequent: pruritus, rash; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, skin hypertrophy, sweating, urticaria, vesiculobullous rash; Rare: melanosis, psoriasis, pustular rash, skin discoloration.

Special senses - Frequent: conjunctivitis; Infrequent: diplopia, dry eyes, photophobia, tinnitus, watery eyes Rare: abnormality of accommodation, blepharitis, cataract specified, corneal erosion, deafness, eye hemorrhage, glaucoma, labyrinthitis, retinal detachment, taste loss, visual field defect.

Urogenital system - Infrequent: bladder pain, breast pain, cystitis, decreased urine stream, dysuria, hematuria, impotence, kidney calculus, kidney pain, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, urinary urgency, vaginitis; Rare: albuminuria, delayed menstrual period, leukorrhea, menopause, urethritis, urinary retention, vaginal hemorrhage.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Sonata is classified as a Schedule IV controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

Abuse

Two studies assessed the abuse liability of Sonata at doses of 25, 50 and 75 mg in subjects with known histories of sedative drug abuse. The results of these studies indicate that Sonata has an abuse potential similar to benzodiazepine and benzodiazepine-like hypnotics.

Dependence

The potential for developing physical dependence on Sonata and a subsequent withdrawal syndrome was assessed in controlled studies of 14- and 28-day durations and in open-label studies of 6- and 12-month durations by examining for the emergence of rebound insomnia following drug discontinuation. Some patients (mostly those treated with 20 mg) experienced a mild rebound insomnia on the first night following withdrawal that appeared to be resolved by the second night. The use of the Benzodiazepine Withdrawal Symptom Questionnaire and examination for any other withdrawal emergent events did not detect any other evidence for a withdrawal syndrome following abrupt discontinuation of Sonata therapy in pre-marketing studies.

However, available data cannot provide a reliable estimate of the incidence of dependence during treatment at recommended doses of Sonata. Other sedative/hypnotics have been associated with various signs and symptoms following abrupt discontinuation, ranging from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Seizures have been observed in two patients, one of which had a prior seizure, in clinical trials with Sonata. Seizures and death have been seen following the withdrawal of zaleplon from animals at doses many times higher than those proposed for human use. Because individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence, they should be under careful surveillance when receiving Sonata or any other hypnotic.

Tolerance

Possible tolerance to the hypnotic effects of Sonata 10 and 20 mg was assessed by evaluating time to sleep onset for Sonata compared to placebo in two placebo-controlled 28-day studies. No development of tolerance to Sonata was observed for time to sleep onset over 4 weeks.

OVERDOSAGE

There is limited pre-marketing clinical experience with the effects of an overdosage of Sonata. Two cases of overdose were reported. One was the accidental ingestion by a 2½ year old boy of 20-40 mg of zaleplon. The second was a 20 year old man who took 100 mg zaleplon plus 2.25 mg of triazolam. Both were treated and recovered uneventfully.

Signs and Symptoms

Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Overdose is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy; in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma, and very rarely death.

Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Animal studies suggest that flumazenil is an antagonist to zaleplon. However, there is no pre-marketing clinical experience with the use of flumazenil as an antidote to a Sonata overdose. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

DOSAGE AND ADMINISTRATION

The dose of Sonata should be individualized. The recommended dose of Sonata for most nonelderly adults is 10 mg. For certain low weight individuals, 5 mg may be a sufficient dose. Although the risk of certain events associated with the use of Sonata appears to be dose dependent, the 20 mg dose has been shown to be adequately tolerated and may be considered for the occasional patient who does not benefit from a trial of a lower dose. Doses above 20 mg have not been adequately evaluated and are not recommended.

Sonata should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep (see Precautions). Taking Sonata with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of Sonata on sleep latency (see Pharmacokinetics under Clinical Pharmacology).

Special Populations

Elderly patients and debilitated patients appear to be more sensitive to the effects of hypnotics, and respond to 5 mg of Sonata. The recommended dose for these patients is therefore 5 mg. Doses over 10 mg are not recommended.

Hepatic insufficiency: Patients with mild to moderate hepatic impairment should be treated with Sonata 5 mg because clearance is reduced in this population. Sonata is not recommended for use in patients with severe hepatic impairment.

Renal insufficiency: No dose adjustment is necessary in patients with mild to moderate renal impairment. Sonata has not been adequately studied in patients with severe renal impairment.

An initial dose of 5 mg should be given to patients concomitantly taking cimetidine because zaleplon clearance is reduced in this population (see Drug Interactions under Precautions). .

HOW SUPPLIED

Sonata capsules are available in bottles of 100 capsules in the following dosage strengths:

5mg, NDC 0008-0925, opaque green cap and opaque pale green body with "5 mg" on the cap and "SONATA" on the body.

10 mg, NDC 0008-0926, opaque green cap and opaque light green body with "10 mg" on the cap and "SONATA" on the body.

The appearance of these capsules is a trademark of Wyeth Laboratories.

STORAGE CONDITIONS
Store at controlled room temperature, 20°-25°C (68°-77°F).
Dispense in a light-resistant container as defined in the USP.

INFORMATION FOR PATIENTS TAKING SONATA

Your doctor has prescribed Sonata to help you sleep. The following information is intended to guide you in the safe use of this medicine. It is not meant to take the place of your doctor's instructions. If you have any questions about Sonata capsules, be sure to ask your doctor or pharmacist.

Sonata is used to treat difficulty in falling asleep. Sonata works very quickly and has its effect during the first part of the night, since it is rapidly eliminated by the body. You should take Sonata immediately before going to bed or after you have gone to bed and are having difficulty falling

asleep. If your principal sleep difficulty is awakening prematurely after falling asleep, there is no evidence that Sonata will be helpful to you. For Sonata to help you fall asleep you should not take it with or immediately after a high-fat/heavy meal.

Sonata belongs to a group of medicines known as the "hypnotics," or simply, sleep medicines. There are many different sleep medicines available to help people sleep better. Sleep problems are usually temporary, requiring treatment for only a short time, usually 1 or 2 days up to 1 or 2 weeks. Some people have chronic sleep problems that may require more prolonged use of sleep medicine. However, you should not use these medicines for long periods without talking with your doctor about the risks and benefits of prolonged use.

Side Effects

All medicines have side effects. The most common side effects of sleep medicines are:

- Drowsiness
- Dizziness
- Lightheadedness
- Difficulty with coordination.

These side effects with Sonata occur most often within an hour after taking it, so it is especially important to take it only when you are about to go to bed or are already in bed.

Sleep medicines can make you sleepy during the day. How drowsy you feel depends upon how your body reacts to the medicine, which sleep medicine you are taking, and how large a dose your doctor has prescribed. Daytime drowsiness is best avoided by taking the lowest dose possible that will still help you sleep at night. Your doctor will work with you to find the dose of Sonata that is best for you. Sonata generally does not cause next-day sleepiness but a few people have reported this.

To manage these side effects while you are taking this medicine:
-- When you first start taking Sonata or any other sleep medicine, until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft.
-- NEVER drink alcohol while you are being treated with Sonata or any sleep medicine. Alcohol can increase the side effects of Sonata or any other sleep medicine.
-- Do not take any other medicines without asking your doctor first. This includes medicines you can buy without a prescription. Some medicines can cause drowsiness and are best avoided while taking Sonata.
-- Always take the exact dose of Sonata prescribed by your doctor. Never change your dose without talking to your doctor first.

Special Concerns

There are some special problems that may occur while taking sleep medicines.

Memory Problems

Sleep medicines may cause a special type of memory loss or "amnesia." When this occurs, a person may not remember what has happened for several hours after taking the medicine. This is usually not a problem since most people fall asleep after taking the medicine. Memory loss can be a problem, however, when sleep medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia." Memory problems are not common while taking Sonata. In most instances memory problems can be avoided if you take Sonata only when you are able to get 4 or more hours of sleep before you need to be active again. Be sure to talk to your doctor if you think you are having memory problems.

Tolerance

When sleep medicines are used every night for more than a few weeks, they may lose their effectiveness to help you sleep. This is known as "tolerance." Development of tolerance to Sonata has not been observed in outpatient clinical studies of up to 4-weeks duration, however, it is unknown if the benefits of Sonata on falling asleep more quickly persist beyond 4 weeks. Sleep medicines should, in most cases, be used only for short periods of time, such as 1 or 2 days and generally no longer than 1 or 2 weeks. If your sleep problems continue, consult your doctor, who will determine whether other measures are needed to overcome your sleep problems.

Dependence

Sleep medicines can cause dependence, especially when these medicines are used regularly for longer than a few weeks or at high doses. Some people develop a need to continue taking their medicines. This is known as dependence or "addiction."

When people develop dependence, they may have difficulty stopping the sleep medicine. If the medicine is suddenly stopped, the body is not able to function normally and unpleasant symptoms (see Withdrawal) may occur. They may find they have to keep taking the medicine either at the prescribed dose or at increasing doses just to avoid withdrawal symptoms.

All people taking sleep medicines have some risk of becoming dependent on the medicine. However, people who have been dependent on alcohol or other drugs in the past may have a higher chance of becoming addicted to sleep medicines. This possibility must be considered before using these medicines for more than a few weeks. If you have been addicted to alcohol or drugs in the past, it is important to tell your doctor before starting Sonata or any sleep medicine.

Withdrawal

Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used daily for a long time. In some cases, these symptoms can occur even if the medicine has been used for only a week or two. In mild cases, withdrawal symptoms may include unpleasant feelings. In more severe cases, abdominal and muscle cramps, vomiting, sweating, shakiness, and rarely, seizures may occur. These more severe withdrawal symptoms are very uncommon. Although withdrawal symptoms have not been observed in the relatively limited controlled trials experience with Sonata, there is, nevertheless, the risk of such events in association with the use of any sleep medicines.

Another problem that may occur when sleep medicines are stopped is known as "rebound insomnia." This means that a person may have more trouble sleeping the first few nights after the medicine is stopped than before starting the medicine. If you should experience rebound insomnia, do not get discouraged. This problem usually goes away on its own after 1 or 2 nights.

If you have been taking Sonata or any other sleep medicine for more than 1 or 2 weeks, do not stop taking it on your own. Always follow your doctor's directions.

Changes in Behavior and Thinking

Some people using sleep medicines have experienced unusual changes in their thinking and/or behavior. These effects are not common. However, they have included:
-- more outgoing or aggressive behavior than normal
-- loss of personal identity
-- confusion
-- strange behavior
-- agitation
-- hallucinations
-- worsening of depression
-- suicidal thoughts

How often these effects occur depends on several factors, such as a person's general health, the use of other medicines, and which sleep medicine is being used. Clinical experience with Sonata suggests that it is uncommonly associated with these behavior changes.

It is also important to realize that it is rarely clear whether these behavior changes are caused by the medicine, an illness, or occur on their own. In fact, sleep problems that do not improve may be due to illnesses that were present before the medicine was used. If you or your family notice any changes in your behavior, or if you have any unusual or disturbing thoughts, call your doctor immediately.

Pregnancy and Breastfeeding

Sleep medicines may cause sedation or other potential effects in the unborn baby when used during the last weeks of pregnancy. Therefore, Sonata is not recommended for use during pregnancy. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking Sonata.

In addition, a very small amount of Sonata may be present in breast milk after use of the medication. The effects of very small amounts of Sonata on an infant are not known; therefore, as with all other hypnotics, it is recommended that you not take Sonata if you are breastfeeding a baby.

Safe Use of Sleeping Medicines

To ensure the safe and effective use of Sonata or any other sleep medicine, you should observe the following cautions:

1. Sonata is a prescription medicine and should be used ONLY as directed by your doctor. Follow your doctor's instructions about how to take, when to take, and how long to take Sonata.
2. Never use Sonata or any other sleep medicine for longer than directed by your doctor.
3. If you notice any unusual and/or disturbing thoughts or behavior during treatment with Sonata or any other sleep medicine, contact your doctor.
4. Tell your doctor about any medicines you may be taking, including medicines you may buy without a prescription. You should also tell your doctor if you drink alcohol. DO NOT use alcohol while taking Sonata or any other sleep medicine.
5. Do not take Sonata unless you are able to get 4 or more hours of sleep before you must be active again.
6. Do not increase the prescribed dose of Sonata or any other sleep medicine unless instructed by your doctor.
7. When you first start taking Sonata or any other sleep medicine, until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft.
8. Be aware that you may have more sleeping problems the first night or two after stopping any sleep medicine.
9. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, if you become pregnant, or are breastfeeding a baby while taking Sonata.
10. As with all prescription medicines, never share Sonata or any other sleep medicine with anyone else. Always store Sonata or any other sleep medicine in the original container and out of reach of children.
11. Be sure to tell your physician if you suffer from depression.
12. Sonata works very quickly. You should only take Sonata immediately before going to bed or after you have gone to bed and are having difficulty falling asleep.

13. For Sonata to work best, you should not take it with or immediately after a high-fat/heavy meal.
14. Some people should start with the lowest dose (5 mg) of Sonata; these include the elderly (i.e., ages 65 and over), and people with liver disease.

END OF DRAFT LABELING

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Exhibit II

U.S. Patent 4,626,538

United States Patent [19]

Dusza et al.

[11] **Patent Number: 4,626,538**

[45] **Date of Patent: * Dec. 2, 1986**

[54] **[7-(3-DISUBSTITUTED AMINO)PHENYL]PYRAZOLO[1,5-A]PYRIMIDINES**

[75] Inventors: **John P. Dusza**, Nanuet, N.Y.; **Andrew S. Tomcufcik**, Old Tappan, N.J.; **Jay D. Albright**, Nanuet, N.Y.

[73] Assignee: **American Cyanamid Company**, Stamford, Conn.

[*] Notice: The portion of the term of this patent subsequent to Jun. 3, 2002 has been disclaimed.

[21] Appl. No.: **732,986**

[22] Filed: **May 13, 1985**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 612,812, May 24, 1984, Pat. No. 4,521,422, which is a continuation-in-part of Ser. No. 506,966, Jun. 23, 1983, abandoned.

[51] **Int. Cl.**[4] **A61K 31/505; C07D 471/04**

[52] **U.S. Cl.** **514/258**; 514/906; 544/281

[58] **Field of Search** 544/281; 514/258

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,178,449	12/1979	Dusza et al.	544/281
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4,576,943	3/1986	Tomcufcik et al.	544/281

Primary Examiner—Donald G. Daus
Assistant Examiner—Stephen M. Kapner
Attorney, Agent, or Firm—Susan H. Rauch

[57] **ABSTRACT**

Novel [7-(3-disubstituted amino)phenyl]pyrazolo[1,5-a]pyrimidines useful as anxiolytic, antiepileptic and sedative-hypnotic agents as well as skeletal muscle relaxants, methods of using these compounds, compositions of matter containing them and processes for their production.

15 Claims, No Drawings

[7-(3-DISUBSTITUTED AMINO)PHENYL]PYRAZOLO[1,5-A]PYRIMIDINES

CROSS REFERENCE TO RELATED APPLICATIONS

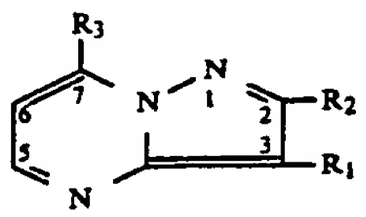
This application is a continuation-in-part of our copending application, U.S. application Ser. No. 612,812, filed May 24, 1984, now U.S. Pat. No. 4,521,422, which is a continuation-in-part of U.S. application Ser. No. 506,966, filed June 23, 1983, now abandoned.

SUMMARY OF THE INVENTION

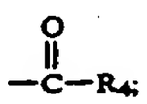
This invention relates to new organic compounds which are [7-(3-disubstituted amino)phenyl]-pyrazolo[1,5-a]pyrimidines, which are useful as anxiolytic and antiepileptic agents as well as sedative-hypnotic agents and skeletal muscle relaxants. This invention also relates to the methods of using the novel compounds, to compositions of matter containing them as the active ingredient and to processes for their production.

DETAILED DESCRIPTION OF THE INVENTION

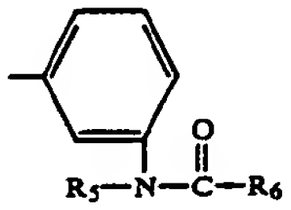
The novel compounds of this invention are represented by the following structural formula:



wherein R_1 is selected from the group consisting of: hydrogen, halogen, cyano and

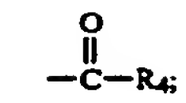


R2 is selected from the group consisting of hydrogen and alkyl(C_1–C_3); R_3 is



R_4 is selected from the group consisting of hydrogen, alkyl(C_1–C_6) and alkoxy(C_1–C_6); R_5 is selected from the group consisting of hydrogen, alkyl(C_1–C_6), alkenyl(C_2–C_6), $-CH_2C{\equiv}CH$, cycloalkyl(C_3–C_6)methyl, $-CH_2OCH_3$ and $-CH_2CH_2OCH_3$; and R_6 is selected from the group consisting of alkyl(C_1–C_6), cycloalkyl(C_3–C_6), —O—alkyl(C_1–C_6), —NH—alkyl(C_1–C_3), —N—dialkyl(C_1–C_3), $-(CH_2)_n$—O—alkyl(C_1–C_3), $-(CH_2)_n$—NH-alkyl(C_1—C_3) and $-(CH_2)_n$—N—dialkyl(C_1–C_3), where n is an integer 1 to 3 inclusive.

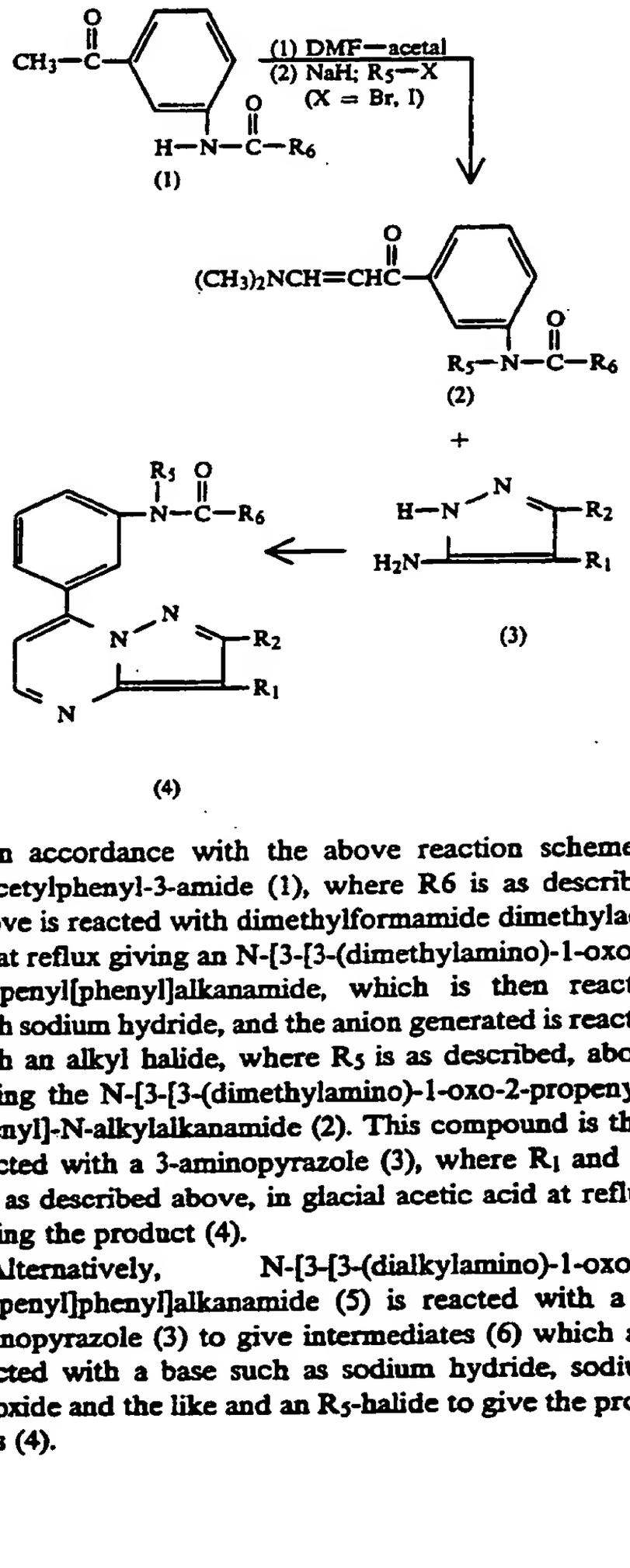
The most preferred compounds of this invention are the compounds of the above formula wherein R_1 is cyano or



R_2 is hydrogen; R_4 is alkyl(C_1–C_6); R_5 is alkyl(C_1–C_6), alkenyl(C_2–C_6) or $-CH_2{\equiv}CH$; and R_6 is alkyl(C_1–C_6), cycloalkyl(C_3–C_6) or —O —alkyl(C_1–C_6).

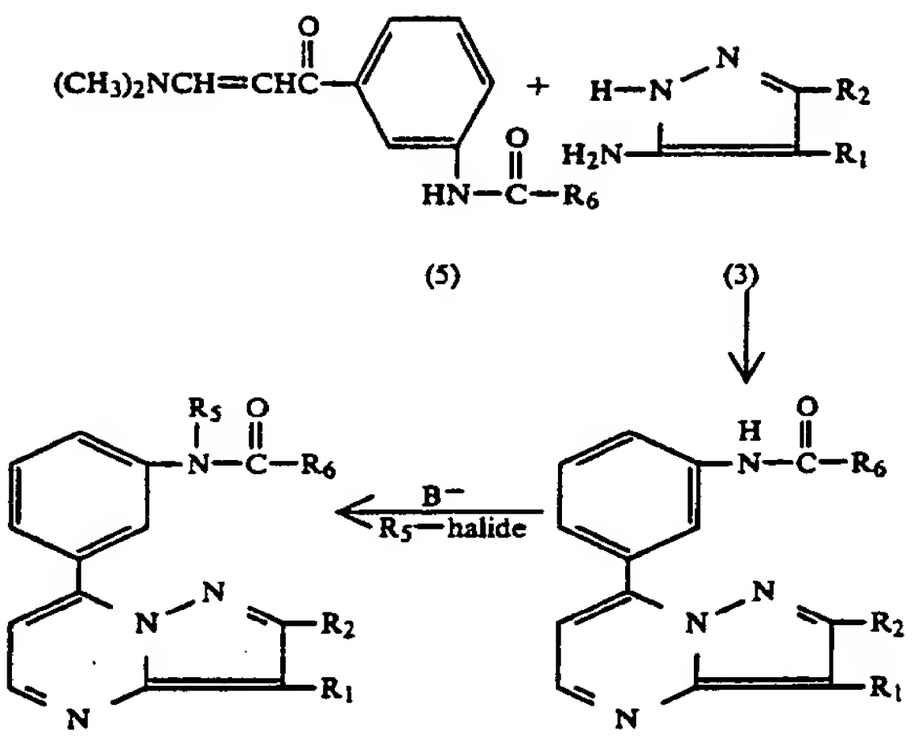
The instant invention is additionally concerned with the methods which employ the above-described compounds in mammals to treat anxiety or epilepsy and to induce a sedative-hypnotic effect or relax skeletal muscles, with compositions of matter containing the above-described compounds and with processes for producing the compounds.

The novel compounds of this invention may be readily prepared as set forth in the following reaction scheme:



In accordance with the above reaction scheme a 1-acetylphenyl-3-amide (1), where R6 is as described above is reacted with dimethylformamide dimethylacetal at reflux giving an N-[3-[3-(dimethylamino)-1-oxo-2-propenyl[phenyl]alkanamide, which is then reacted with sodium hydride, and the anion generated is reacted with an alkyl halide, where R_5 is as described, above giving the N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]-phenyl]-N-alkylalkanamide (2). This compound is than reacted with a 3-aminopyrazole (3), where R_1 and R_2 are as described above, in glacial acetic acid at reflux, giving the product (4).

Alternatively, N-[3-[3-(dialkylamino)-1-oxo-2-propenyl]phenyl]alkanamide (5) is reacted with a 3-aminopyrazole (3) to give intermediates (6) which are reacted with a base such as sodium hydride, sodium alkoxide and the like and an R_5-halide to give the products (4).



Details of the preparative scheme are fully apparent from the U.S. Pat. No. 4,521,422, which is hereby incorporated by reference.

The performance of the novel compounds of the present invention in standard tests with laboratory animals which are known to correlate well with relief of anxiety in man indicates that they possess central nervous system activity at nontoxic doses and thus are useful as anxiolytic agents. Furthermore, these compounds have been shown by biological data to be useful as antiepileptic agents, particularly in the treatment of grand mal epilepsy seizures, and as sedative-hypnotic and skeletal muscle relaxant agents.

The anti-anxiety and anticonvulsant properties of the novel compounds of the present invention have been established in a test which indicates anxiolytic and antiepileptic activity by the measure of protection they provide from convulsions resulting from the administration of pentylenetetrazole. Single or graded dose levels of the test compounds were administered orally or intraperitoneally in a 2% starch vehicle, containing 0.5% v/v polyethylene glycol and one drop of Polysorbate 80 to groups of at least 4 rats. At 30 or 60 minutes, the rats were treated intravenously with pentylenetetrazole at a dose of 23 mg/kg of body weight. This dose is estimated to cause clonic seizures in 99% of unprotected rats. It has been reported [R. T. Hill and D. H. Tedeschi, "Animal Testing and Screening Procedures in Evaluating Psychotropic Drugs" in "An Introduction to Psychopharmacology", Eds. R. R. Rech and K. E. Moore, Raven Press, New York, p. 237–288 (1971)] that there is a high degree of correlation between the ability of compounds to inhibit the seizure-inducing effect of pentylenetetrazole in rats and the effectiveness of those compounds as anxiolytic and anticonvulsive agents in higher warm-blooded animals. The results of this test on representative compounds of the present invention are shown in Table I.

TABLE I

Compound	Dose (mg/kg)	% of Rats Protected
Protection Against Clonic Seizures Caused by Pentylenetetrazole in Rats		
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylpropanamide	25.0	100
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	25.0	100
N—[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	25.0	100
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—propylacetamide	6.25	100
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester	3.1	25
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester	12.6	75
N—butyl-N—[3-(3-cyanopyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]acetamide	25.0	50
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester	25.0	25
[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester	25.0	25
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propenylacetamide	25.0	100
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propynylacetamide	6.25	100
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylcyclobutanecarboxamide	25.0	50
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylcyclopropanecarboxamide	25.0	75
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	25.0	75
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	12.5	50
7-[3-(acetylmethylamino)phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	25.0	100
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylpropanamide	12.5	50
N—[3-(3-cyano-2-methylpyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]-N—methylpropanamide	25.0	100

Another test which has been used to assess antianxiety effects is a nonconditioned passive avoidance procedure described by J. R. Vogel, B. Beer and D. E. Clody, "A Simple and Reliable Conflict Procedure for Testing Anti-Anxiety Agents", Psychopharmacologia, 21, 1–7 (1971). A conflict situation is induced in rats by a modification of this method.

Groups of 6 native, Wistar strain rats, weighing 200–240 g each were deprived of water for 48 hours and food for 24 hours. The test compounds were administered in single or graded, oral or intraperitoneal doses, suspended in a 2% starch vehicle containing 0.5% v/v polyethylene glycol and one drop of polysorbate 80. Control animals received the vehicle alone. At 30 to 60 minutes each rat was placed in an individual plexiglass chamber. Water was available ad libitum from a tap located in the rear of the chamber. A 0.7 milliampere DC shocking current was established between the stainless steel grid floor and the tap. After 20 licks of nonshocked drinking, a shock was delivered for 2 seconds and then further shocks were delivered on a ratio of one shock for 2 seconds for every 20 licks. This was continued for a total of 3 minutes. The number of shocks taken by each rat during the 3 minute interval was recorded and compared to a control group. The test compounds are considered active if the number of shocks received by the test group is significantly higher than the control group by the Mann-Witney U test. Results of this test on

representative compounds of this invention appear in Table II.

TABLE II

Nonconditioned Passive Avoidance Test in Rats		
Compound	Dose (mg/kg)	Result
N—3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylpropanamide	0.4	Active
N—3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]N—ethylacetamide	0.8	Active
N—ethyl-N—(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide	25.0	Active
N—[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	3.1	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—propylacetamide	1.5	Active
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester	3.1	Active
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester	12.5	Active
[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester	25.0	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propenylacetamide	3.1	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propynylacetamide	1.5	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylpropaneamide	6.2	Active
N—[3-(3-cyano-2-methylpyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]-N—methylpropanamide	25.0	Active
7-[3-(acetylmethylamino)phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	25.0	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	1.5	Active
N—[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	3.1	Active
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylcyclobutanecarboxamide	25.0	Active

Another test utilized for the determination of anxiolytic activity is the measurement of the ability of test compounds to inhibit the binding of tritiated benzodiazepines to brain-specific receptors of warm-blooded animals. A modification of the method described by R. F. Squires, et al., Nature, 266, No. 21, p. 732 (April 1977) and H. Mohler, et al., Science, 198, p. 849 (1977) was employed.

Male albino rats (Wistar strain, weighing 150–200 g each) were obtained from Royalhart Farms. ^{3}H-Methyldiazepam (79.9 Ci/mmol) and ^{3}H-methylflunitrazepam (84.3 Ci/mmol) were obtained from New England Nuclear. The test compounds were solubilized in either dimethylformamide, acetic acid, ethanol or hydrochloric acid.

Whole cortex of rats was homogenized gently in 20 volumes of ice-cold 0.32 M sucrose, centrifuged twice at 1000 g for 10 minutes and then recentrifuged at 30,000 g for 20 minutes to produce a crude P_2-synaptosomal fraction. The P_2-fraction was either: (1) resuspended in twice the original volume in hypotonic 50 mM Tris.HCl (pH 7.4), or (2) resuspended in one-half the original volume in hypotonic 10 mM Tris.HCl (pH 7.4) and then was frozen (−20° C.) until time of use. Frozen P_2 preparations were thawed and resuspended in four times the original homogenizing volume at time of assay.

The binding assay consisted of 300 μl of the P_2-fraction suspension (0.2–0.4 mg protein), 100 μl of test drug and 100 μl of ^{3}H-diazepam (1.5 nM, final concentration) or ^{3}H-flunitrazepam (1.0 nM, final concentration) which was added to 1.5 ml of 50 mM Tris.HCl (pH 7.4). Non-specific binding controls and total binding controls received 100 μl of diazepam (3 M, final concentration) and 100 μl of deionized water, respectively, in place of the test compound. Incubation for 30 minutes proceeded in ice and was terminated by filtration, under vacuum, through Whatman GF/C glass fiber filters. The filters were washed twice with 5 ml of ice-cold 50 mM Tris.HCl (pH 7.4) and placed in scintillation vials. After drying at 50°–60° C. for 30 minutes, 10 ml of Beckman Ready-Solv TM HP (a high performance premix scintillation cocktail, registered trademark of Beckman Instruments, Inc., Irvine, CA 92713) was added and the radioactivity determined in a scintillation counter.

Inhibition of binding was calculated by the difference between total binding and binding in the presence of test compound, divided by the total binding × 100.

The results of this test on representative compounds of the present invention are given in Table III.

TABLE III

Inhibition of the Binding of ^{3}H—Benzodiazepine to Brain-Specific Receptors of Rats	
Compound	% Inhibition
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylpropanamide	83
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	79
N—[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	97
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—propylacetamide	64
7-[3-[ethyl(1-oxopropyl)amino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	100
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]methylcarbamic acid, methyl ester	87
7-[3-[(methoxycarbonyl)methylamino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	98
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]ethylcarbamic acid, methyl ester	55
7-[3-[ethyl(methoxycarbonyl)amino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	99
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]methylcarbamic acid, methyl ester	41
ethyl(3-pyrazolo[1,5-a]pyrimidin-7-yl-phenyl)carbamic acid, ethyl ester	61
[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]ethylcarbamic acid, ethyl ester	63
[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]ethylcarbamic acid, ethyl ester	78
[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]ethylcarbamic acid, ethyl ester	78
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propenylacetamide	91
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—2-propynylacetamide	42
N—[3-(3-cyano-2-methylpyrazolo[1,5-a] pyrimidin-7-yl)phenyl]propanamide	79
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylpropanamide	95
N—[3-(3-cyano-2-methylpyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]-N—methylpropanamide	54
N—methyl-N—(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide	100
7-[3-(acetylmethylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	73
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	71
N—[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	81
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl[-N—methylcyclobutanecarboxiamde	83
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-	

TABLE III-continued

Inhibition of the Binding of ^3H—Benzodiazepine to Brain-Specific Receptors of Rats	
Compound	% Inhibition
yl)phenyl]-N—methylcyclopropanecarboxamide	
7-[3-[(cyclopropylcarbonyl)methylamino]-phenylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	95
7-[3-(acetylethylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	97
7-[3-(acetylamino)phenyl]pyrazolo[1,5-a]-pyrimidine-3-carboxylic acid, ethyl ester	85
7-[3-[(methoxycarbonyl)amino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	76
methyl(3-pyrazolo[1,5-a]pyrimidin-7-yl-phenyl)carbamic acid, methyl ester	45
7-[3-(acetylpropylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	97
[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester	92
7-[3-[(cyclobutylcarbonyl)amino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	82

The novel compounds of this invention have also been shown to have skeletal muscle relaxant activity through the use of two tests. The first test measures the effect of representative compounds on the ability of rats to remain on an inclined screen. Groups of at least 6 rats were treated orally with graded doses of test compounds or vehicle and placed on a wire mesh screen (inclined at an angle of 60° from a horizontal level) 65 minutes later. The number of rats falling off the screen within 30 minutes was recorded. The ED_{50} (dose necessary to cause 50% of the animals tested to fall off) was calculated according to the linear arcsine transformation method of Finney, D. J., "Statistical Methods in Biological Assay", 2nd Ed., Hafner, N.Y., 1964, p. 454. Compounds were dissolved or suspended in a 2% aqueous starch suspension containing 5% polyethylene glycol 400 and a drop of polysorbate 80, and administered in a constant volume of 5 ml/kg. The results of representative compounds of this invention appear in Table IV.

TABLE IV

Effect on Ability of Rats to Remain on an Inclined Screen	
Compound	ED_{50} (mg/kg)
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylpropanamide	4.6
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	3.9

The second test to illustrate that the novel compounds of the present invention possess skeletal muscle relaxant properties shows the effect of representative compounds on the locomotor activity in rats. Groups of 6 rats were treated orally with vehicle (5 ml/kg) or graded doses of the test compounds. Sixty minutes later, individual rats were placed in Actophotometers and locomotor activity was measured for 5 minutes after a brief (30 sec.) habituation period. Motor activity counts (number of crossings of the photo cells) were recorded for each rat, and mean activity counts were calculated for each treatment group. The dose causing a 50% decrease in mean activity counts compared with the vehicle group (MDD_{50}) was calculated from a linear regression equation. The test results of representative compounds appear in Table V.

TABLE V

Effects on Locomotor Activity in Rats	
Compound	MDD_{50} (mg/kg P.O.)
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylpropanamide	2.0
N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	1.4

The novel compounds of the present invention have been found to be highly useful for drug therapy in mammals when administered in amounts ranging from about 0.1 mg to about 20.0 mg/kg of body weight per day. A preferred dosage regimen for optimum results would be from about 0.5 mg to about 10.0 mg/kg of body weight per day. Dosage units are employed such that a total of from about 10 to about 700 mg of active compound for a subject of about 70 kg of body weight are administered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of this invention are preferably administered orally but may be administered in any convenient manner such as by the intravenous, intramuscular, or subcutaneous routes.

Compositions according to the present invention having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.10% to 10.0% by weight of active compound in a vehicle consisting of a polyhydric aliphatic alcohol or mixtures thereof. Especially satisfactory are glycerin, propylene glycol, and polyethylene glycols. The polyethylene glycols consist of a mixture of nonvolatile, normally liquid, polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from about 200 to 1500. Although the amount of active compound dissolved in the above vehicle may vary from 0.10% to 10.0% by weight, it is preferred that the amount of active compound employed be from about 3.0% to about 9.0% by weight. Although various mixtures of the aforementioned nonvolatile polyethylene glycols may be employed, it is preferred to use a mixture having an average molecular weight of from about 200 to about 400.

In addition to the active compound, the parenteral solutions may also contain various preservatives which may be used to prevent bacterial and fungal contamination. The preservatives which may be used for these purposes are, for example, myristyl-gamma-picolinium chloride, benzalkonium chloride, phenethyl alcohol, p-chlorophenyl-alpha-glycerol ether, methyl and propyl parabens, and thimerosal. As a practical matter, it is also convenient to employ antioxidants. Suitable antioxidants include, for example, sodium bisulfite, sodium metabisulfite, and sodium formaldehyde sulfoxylate. Generally, from about 0.05% to about 0.2% concentrations of antioxidant are employed.

For intramuscular injection, the preferred concentration of active compound is 0.25 to 0.50 mg/ml of the final compositions. The novel compounds of the present invention are equally adapted to intravenous administration when diluted with water or diluents employed in intravenous therapy such as isotonic glucose in appro-

priate quantities. For intravenous use, initial concentrations down to about 0.05 to 0.25 mg/ml of active ingredient are satisfactory.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or compressed into tablets, or incorporated directly into the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Additionally, the active ingredient may be incorporated with the proper pharmaceutical carrier or carriers known in the art to produce a sustained-release tablet or capsule. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit dose. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a wetting agent such as sodium lauryl sulfate and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially nontoxic in the amounts employed.

The following non-limiting examples illustrate the preparation of representative compounds of the present invention.

EXAMPLE 1

N-[3-[3-(Dimethylamino)-1-oxo-2-propenyl]phenyl]-propanamide

A 20 g portion of N-(3-acetylphenyl)propanamide in 50 ml of dimethylformamide dimethylacetal was refluxed for 8 hours, then evaporated. The residue was taken up in 200 ml of dichloromethane, passed through hydrous magnesium silicate, diluted with hexane and concentrated, giving 21.17 g of the desired compound.

Following the procedure of Example 1 and using the indicated starting materials, the amides of Examples 2–5, found in Table VI, were prepared.

TABLE VI

Ex.	Starting Material	Amide
2	N—(3-acetylphenyl)-ethanamide	N—[3-(3-dimethylamino)-1-oxo-2-propenyl)phenyl]-acetamide
3	(3-acetylphenyl)carbamic acid, methyl ester	[3-[3-dimethylamino)-1-oxo-2-propenyl]phenyl]-carbamic acid, methyl ester
4	(3-acetylphenyl)carbamic acid, butyl ester	[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-carbamic acid, butyl ester
5	N—(3-acetylphenyl)-butanamide	N—[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-butanamide

EXAMPLE 6

N-[3-[3-(Dimethylamino)-1-oxo-2-propenyl]phenyl-N-ethylpropanamide

A mixture of 3.47 g of N-[3-[3-(dimethylamino)-oxo-2-propenyl]phenyl]propanamide and 0.68 g of 60% sodium hydride in oil in dimethylformamide was stirred for 0.5 hour under argon, then cooled in an ice bath and a solution of 2.4 g of ethyl iodide in 10 ml of dimethylformamide was added in small portions. The mixture was then stirred at room temperature for 0.5 hour and extracted three times with hexane. The extracts were discarded, water was added and this mixture extracted with dichloromethane. This extract was evaporated and the residue crystallized from hexane giving the desired compound, mp 105°–107° C.

Following the procedure of Example 6 using the compounds of Examples 1–5 and appropriate alkyl halides, the alkylated amides of Examples 7–12, found in Table VII, were prepared.

TABLE VII

Ex.	Starting Material of Ex.	Alkylated Amide	MP °C.
7	2	N—[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N—ethylacetamide	110–113
8	1	N—[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N—methylpropanamide	148–149
9	2	N—[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N—propylacetamide	110–112
10	3	[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]methylcarbamic acid, methyl ester	93–95
11	3	[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]ethylcarbamic acid, methyl ester	95–97
12	2	N—[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N—methylacetamide	146–148

EXAMPLE 13

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylpropanamide

A mixture of 0.54 g of 3-amino-4-pyrazolecarbonitrile and 1.37 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylpropanamide in 50 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed. The residue was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was separated, dried, passed through a pad of hydrous magnesium silicate and hexane was added to the refluxing filtrate. The mixture was then cooled and the solid collected, giving 1.3 g of the desired product, mp 161°–162° C.

Following the procedure of Example 13 and using appropriately substituted 3-amino-pyrazoles together

with the indicated intermediates, the products of Examples 14–37 found in Table VIII were prepared.

TABLE VIII

Ex.	Intermediate of Ex.	3-Amino-pyrazole	Product	MP °C.
14	7	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—ethylacetamide	186–187
15	7	3-aminopyrazole	N—ethyl-N—(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide	115–117
16	9	3-aminopyrazole	N—propyl-N—(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide	90–92
17	9	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—propylacetamide	151–153
18	6	ethyl-3-amino-pyrazole-4-carboxylate	7-[3-[ethyl(1-oxopropyl)amino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	124–126
19	10	3-aminopyrazole-4-carbonitrile	[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester	168–170
20	10	ethyl-3-amino-pyrazole-4-carboxylate	7-[3-[(methoxycarbonyl)methyl-amino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	115–116
21	3	3-aminopyrazole-4-carbonitrile	[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]carbamic acid, methyl ester	256–258
22	4	3-aminopyrazole-4-carbonitrile	[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]carbamic acid, butyl ester	131–133
23	1	3-aminopyrazole	N—[3-(pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]propanamide	177–178
24	1	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]propanamide	202–204
25	1	3-amino-5-methylpyrazole-4-carbonitrile	N—[3-(3-cyano-2-methylpyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]propanamide	177–178
26	8	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylpropanamide	
27	8	3-amino-5-methylpyrazole-4-carbonitrile	N—[3-(3-cyano-2-methylpyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]-N—methyl-propanamide	184–186
28	5	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]butanamide	138–140
29	12	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N—methylacetamide	195–197
30	2	3-aminopyrazole-4-carbonitrile	N—[3-(3-cyanopyrazolo[1,5-a]pyrimidine-7-yl)phenyl]acetamide	257–259
31	12	3-aminopyrazole	N—methyl-N—(3-pyrazolo[1,5-a]pyrimidine-7-ylphenyl)acetamide	118–120
32	12	ethyl-3-amino-pyrazole-4-carboxylate	7-[3-(acetylmethylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	155–156
33	7	3-amino-4-carbo-ethoxypyrazole	7-[3-(acetylethylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	147–148
34	2	3-amino-4-carbo-ethoxypyrazole	7-[3-(acetylamino)phenyl]pyrazolo[1,5-a]-pyrimidine-3-carboxylic acid, ethyl ester	202–204
35	3	3-amino-4-carbo-ethoxypyrazole	7-[3-[(methoxycarbonyl)amino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	187–188
36	10	3-aminopyrazole	methyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, methyl ester	107–109
37	9	3-amino-4-carbo-ethoxypyrazole	7-[3-(acetylpropylamino)phenyl]pyrazolo-[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester	156–157

EXAMPLE 38

N-[3-(3-Chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide

A mixture of 1.0 g of N-ethyl-N-(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide and 4.57 g of 1-chlorobenzotriazole in 50 ml of dichloromethane was refluxed for 25 minutes, then cooled and poured into 50 ml of ice-cold 2.5N aqueous sodium hydroxide. The mixture was filtered through hydrous magnesium silicate, precipitated with hexane and the solid collected, giving 0.7 g of the desired product, mp 157°–159°C.

EXAMPLE 39

7-[3-[Ethyl(methoxycarbonyl)amino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester

A 12.41 g portion of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]carbamic acid, methyl ester was reacted as described in Example 6, using 9.36 g of ethyliodide, giving 13.4 g of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]ethylcarbamic acid, methyl ester, mp 95°–97° C.

A 2.76 g portion of the above ester was reacted with 1.55 g of ethyl-3-aminopyrazole-4-carboxylate as described in Example 13, giving 2.87 g of the desired product, mp 117°–119 C.

EXAMPLE 40

[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester

A 2.76 g portion of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]ethylcarbamic acid, methyl ester was reacted with 1.08 g of 3-aminopyrazole-4-carbonitrile as described in Example 13, giving 2.6 g of the desired product, mp 162°–164° C.

EXAMPLE 41

[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, ethyl ester

1-Acetylphenyl-3-carbamic acid, ethyl ester was converted to [3-[3-(dimethylamino)-1-oxo-2-propenyl]-phenyl]carbamic acid, ethyl ester by the procedure of Example 1 and this ester was then reacted with methyl iodide, again by the procedure of Example 6, giving [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]methylcarbamic acid, ethyl ester.

A 2.6 g portion of the above ester was reacted with 1.08 g of 3-aminopyrazole-4-carbonitrile by the procedure of Example 13, giving 2.09 g of the desired compound, mp 140°–142° C.

EXAMPLE 42

Ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester

[3-[3-(Dimethylamino)-1-oxo-2-propenyl]phenyl]carbamic acid was reated with ethyl iodide by the procedure of Example 6, giving [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]ethylcarbamic acid, ethyl ester.

A 2.9 g portion of the above ester was reacted with 0.83 g of 3-aminopyrazole by the procedure of Example 13, giving 2.27 g of the desired product, mp 79°–81° C.

EXAMPLE 43

[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester

A 2.0 g portion of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]ethylcarbamic acid, ethyl ester was reacted with 1.08 g of 3-aminopyrazole-4-carbonitrile as described in Example 13, giving 2.52 g of the desired product, mp 133°–135° C.

EXAMPLE 44

[3-(3-Chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester

A 1.55 g portion of ethyl(3-pyrazolo[1,5-a]-pyrimidin-7-ylphenyl)carbamic acid, ethyl ester in 50 ml of dichloromethane was reacted with 1-chlorobenzotriazole for 30 minutes, giving 1.29 g of the desired product, mp 100°–102° C.

EXAMPLE 45

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide

An 11.61 g portion of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]acetamide was reacted with 7.26 g of allyl bromide as described in Example 6, giving 13.34 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-2-propenylacetamide, mp 91°–94° C.

A 1.36 g portion of the above intermediate was reacted with 0.54 g of 3-aminopyrazole-4-carbonitrile as described in Example 13, giving 1.0 g of the desired compound, mp 135°–137° C.

EXAMPLE 46

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide

An 11.61 g portion of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]acetamide was reacted with propynyl bromide as described in Example 6, giving N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-2-propynylacetamide, mp 98°–101° C.

A 2.7 g portion of the above intermediate was reacted with 1.08 g of 3-aminopyrazole-4-carbonitrile as described in Example 13, giving 1.90 g of the desired product, mp 193°–195° C.

EXAMPLE 47

N-Butyl-N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]acetamide

An 11.61 g portion of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]carbamic acid, methyl ester was reacted with 11.0 g of butyl iodide by the procedure of Example 6, giving 16.3 g. of N-butyl-N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]acetamide.

A 2.88 g portion of the above intermediate was reacted with 1.08 g of 3-aminopyrazole-4-carbonitrile by the procedure of Example 13, giving 1.61 g of the desired product, mp 146°–148° C.

EXAMPLE 48

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcarbamic acid, butyl ester

An 11.61 g portion of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]carbamic acid, butyl ester was reacted with 6.82 g of methyl iodide by the procedure of Example 6, giving 11.67 g of [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]methylcarbamic acid, butyl ester.

A 3.04 g portion of the above ester was reacted with 1.08 g of 3-aminopyrazole-4-carbontirile as described in Example 13, giving 2.3 g of the desired product, mp 96°–97° C.

EXAMPLE 49

N-[3-(3-Chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide

A 1.0 g portion of N-methyl-N-(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)acetamide was reacted as described in Example 38, giving 1.0 g of the desired product, mp 163°–165° C.

EXAMPLE 50

[3-(3-Chloropyrazolo1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester

A 1.4 g portion of methyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, methyl ester was reacted as described in Example 38, giving 1.42 g of the desired product, mp 132°–134° C.

EXAMPLE 51

7-[3-[(Cyclopropylcarbonyl)methylamino]phenyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester

N-(3-Acetylphenyl)cyclopropanecarboxamide was prepared by the reaction of m-aminoacetophenone, diisopropylethylamine and cyclopropanecarboxylic acid chloride in dichloromethane.

This compound was then converted to N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]cyclopropanecarboxamide by the procedure of Example 1 and then alkylated by the procedure of Example 6, using methyl iodide, giving 10.17 g of N-[3-(3-dimethylamino)-1-oxo-2-propenyl)phenyl]-N-methylcyclopropanecarboxamide, mp 120°–122° C.

A 0.54 g portion of this compound was reacted as described in Example 13 with 3-aminopyrazole-4-carbonitrile, giving 1.08 g of the desired product, mp 178°–180° C.

EXAMPLE 52

7-[3-[(Cyclopropylcarbonyl)methylamino]phenyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester

A 0.73 g portion of ethyl 3-aminopyrazole-4-carboxylate and 1.36 g of N-[3-[(3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylcyclopropanecarboxamide were reacted as described in Example 13, giving 0.52 g of the desired product, mp 122°–124° C.

EXAMPLE 53

N-[3-(3-Cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide

m-Aminoacetophenone, cyclobutanecarboxylic acid, chloride and diisopropylethylamine in dichloromethane were reacted, giving N-(3-acetylphenyl)cyclobutanecarboxamide.

This compound was then converted to N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]cyclobutanecarboxamide, mp 155°–157° C., by the procedure of Example 1 and further alkylated by the procedure of Example 6, using methyl iodide to give 8.32 g of N-[3-[3-(dimethylamino)1-oxo-2-propenyl]phenyl]-N-methylcyclobutanecarboxamide, mp 117°–119° C.

A 0.54 g portion of 3-aminopyrazole-4-carbonitrile was reacted with 1.43 g of the above product by the procedure of Example 13, giving 1.3 g of the desired product, mp 157°–158° C.

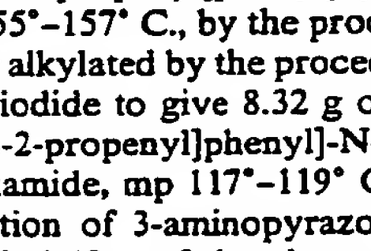
EXAMPLE 54

7-[3-[(Cyclobutylcarbonyl)amino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester

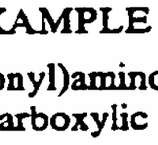
A 0.78 g portion of 3-amino-4-carboethoxypyrazole ard 1.36 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]cyclobutanecarboxamide were reacted as described in Example 13, giving 1.52 g of the desired product, mp 123°–125° C.

What is claimed is:

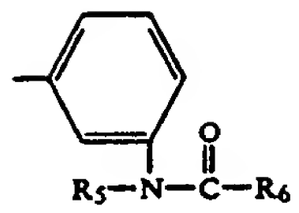
1. A compound of the formula:



wherein R_1 is selected from the group consisting of hydrogen, halogen, cyano and

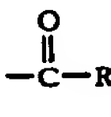


R_2 is selected from the group consisting of hydrogen and alkyl (C_1–C_3); R_3 is



R_4 is selected from the group consisting of hydrogen, alkyl(C_1–C_6) and alkoxy(C_1–C_6); R_5 is selected from the group consisting of hydrogen, alkyl(C_1–C_6), alkenyl(C_2–C_6), $-CH_2C{\equiv}CH$, cycloalkyl(C_3–C_6)methyl, $-CH_2OCH_3$ and $-CH_2CH_2OCH_3$; and R_6 is selected from the group consisting of alkyl(C_1–C_6), cycloalkyl(C_3–C_6), —O-alkyl(C_1–C_6), —NH-alkyl(C_1–C_3), —N-dialkyl(C_1–C_3), $-(CH_2)_n$—O-alkyl(C_1–C_3), $-(CH_2)_n$—NH-alkyl(C_1–C_3) and $-(CH_2)_n$—N-dialkyl(C_1–C_3), where n is an integer 1 to 3 inclusive.

2. A compound according to claim 1, wherein R_1 is cyano or



R_2 is hydrogen; R_4 is alkyl(C_1–C_6), alkenyl(C_2–C_6) or $-CH_2{\equiv}CH$; and R_6 is alkyl (C_1–C_6), cycloalkyl(C_3–C_6) or —O-alkyl(C_1–C_6).

3. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylpropanamide.

4. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide.

5. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-propylacetamide.

6. The compound according to claim 2, which is [3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester.

7. The compound according to claim 2, which is 7-[3-[(methoxycarbonyl)methylamino]phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester.

8. The compound according to claim 2, which is [3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester.

9. The compound according to claim 2, which is ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester.

10. The compound according to claim 2, which is [3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester.

11. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide.

12. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide.

13. The compound according to claim 2, which is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide.

14. A method of ameliorating anxiety in a mammal which comprises administering to said mammal an amount of a compound of claim 1 sufficient to reduce anxiety.

15. A composition of matter in dosage unit form comprising from 2–750 mg of a compound of claim 1 in association with a pharmaceutically acceptable carrier.

* * * * *

Exhibit III

Maintenance Fee Payments for US Patent 4,626,538

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Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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PAYOR NUMBER
000142

75L8/0606

MAUREEN GUADAGNO
PATENT LAW DEPT.
AMERICAN CYANAMID COMPANY
ONE CYANAMID PLAZA
WAYNE, NJ 07470-8426

Amp
2094

DATE MAILED
06/06/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,626,538	184	1870	----	06/732,986	12/02/86	05/13/85	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	29.995

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MS.KAY E. BRADY
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MADISON NJ 07940-0874

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If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,626,538	185	3160	----	06/732,986	12/02/86	05/13/85	12	NO	PAID

RECEIVED
JUN 22 1998
PATENT LAW DEPT.

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	29,995

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☆ U.S. GPO: 1998-437-690/73138

Exhibit IV

(a) Terminal Disclaimer
(b) Request for Certificate of Correction
(c) Decision Granting Petition for Certificate of Correction

29,995

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JOHN PAUL DUSZA,
ANDREW STEPHEN TOMCUFCIK and
JAY DONALD ALBRIGHT

Serial No.: 732,986 Group Art Unit: 122

Filed: May 13, 1985 Examiner: S. Kapner

For: [7-(3-DISUBSTITUTED AMINO)-PHENYL]PYRAZOLO[1,5-a]-PYRIMIDINES

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

S I R :

TERMINAL DISCLAIMER PURSUANT
TO 37 C.F.R. 1.321(b)

Your petitioner, AMERICAN CYANAMID COMPANY, a corporation organized and existing under the laws of the State of Maine and having its executive offices at One Cyanamid Plaza, Wayne, in the County of Passaic and State of New Jersey, represents that it is the assignee of the entire right, title and interest in application Serial No. 732,986, filed May 13, 1985, for [7-(3-DISUBSTITUTED AMINO)PHENYL]PYRAZOLO[1,5-a]PYRIMIDINES by an assignment recorded in the United States Patent and Trademark Office on May 13, 1985.

Your petitioner, AMERICAN CYANAMID COMPANY, hereby disclaims the terminal part of any patent granted on the above-identified application which would extend beyond June 3, 2002, and hereby agrees that any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to United States Letters Patent No. 4,521,422 and to any patent which might issue on application Serial No. 732,985; this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors or assigns.

AMERICAN CYANAMID COMPANY

By John J. Hagan
John J. Hagan, Manager
Patent Law Department

Signed at Stamford in the
County of Fairfield and State
of Connecticut this 21st
day of April, 1986.

KEM

ST-82 11/79

PATENT
Attorney Docket No. 1142.0068-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,626,538

Inventors: Dusza et al.

Issue Date: December 2, 1986

Assigned: American Cyanamid Company

For: [7-(3-DISUBSTITUTED AMINO)PHENYL] PYRAZOLO[1,5-A]PYRIMIDINES

Attn: Office of Petitions
Crystal Plaza 4-3C23

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 35 U.S.C. § 254, OR IN THE ALTERNATIVE, A PETITION UNDER 37 C.F.R. § 1.182 TO RESET THE EFFECT OF A TERMINAL DISCLAIMER IN ACCORDANCE WITH 35 U.S.C. § 154(c)(1)

American Cyanamid Company is the owner of the above-identified patent by virtue of an Assignment recorded in the U.S. Patent and Trademark Office (PTO) on May 13, 1985 at Reel 4406, Frame 0769. The Commissioner is requested to issue a Certificate of Correction or take other appropriate action to indicate a portion of the term of U.S. Patent No. 4,626,538 subsequent to the expiration date of U.S. Patent No. 4,521,422 has been disclaimed.

A power of attorney and statement under 37 C.F.R. § 3.73(b) is attached (Exhibit A).

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Although no fee is required to consider and grant a Certificate of Correction under 35 U.S.C. § 254, any fees necessary for consideration of this request should be charged to Deposit Account No. 06-0916.

I. Grant of U.S. Patent No. 4,626,538

U.S. Patent 4,626,538 (Exhibit B) was granted on December 2, 1986 on Application Serial No. 732,986 filed May 13, 1985. The 1985 application is a continuation-in-part of Application Serial No. 612,812 filed May 24, 1984, now U.S. Patent No. 4,521,422 (Exhibit C), which in turn is a continuation-in-part of Application Serial No. 506,966 filed June 23, 1983, now abandoned.

In an Office Action mailed November 22, 1985 (Exhibit D), in Serial No. 732,986, the PTO rejected claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 4,521,422. Claims were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 and 18 of copending Application Serial No. 732,985. Applicants timely responded to the double patenting rejections by filing a terminal disclaimer (Exhibit E) pursuant to 35 U.S.C. § 253 and 37 C.F.R. § 1.321(b). In pertinent part, the terminal disclaimer contained the following statement:

> Your petitioner, AMERICAN CYANAMID COMPANY, hereby disclaims the terminal part of any patent granted on the above-identified application which would extend beyond June 3, 2002, and hereby agrees that any patent so granted on the above-identified application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to United States Letters Patent No. 4,521,422 and to any patent which might issue on application Serial No. 732,985; this agreement to run with any patent granted on the above-identified application and to be binding upon the grantee, its successors or assigns.

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In remarks accompanying the response filed April 23, 1986 (Exhibit F) to the PTO action mailed November 22, 1985, applicants indicated that the terminal disclaimer was being filed to overcome the double patenting rejections. The text of the remarks in that response is as follows:

> Claims 1-14 and 18 are rejected as double patenting of the obviousness type over U.S. Patent No. 4,521,422 and provisionally rejected as double patenting of the obviousness type over their copending Application Serial No. 732,985. To overcome these rejections, pursuant to 37 C.F.R. § 1.321(b), Applicants are submitting herewith Assignee's disclaimer of the term of any patent granted on the above-identified Application which would extend beyond the expiration date of U.S. Patent No. 4,521,422 (June 3, 2002) and Assignee's acknowledgment that any patent granted on said Application would be enforceable only for such time as its legal title is identical to the legal title of U.S. Patent No. 4,521,422 and to any patent which might issue on Application Serial No. 732,985.
>
> In view of the terminal disclaimer, Claims 1-14 and 18 are patentable over U.S. Patent No. 4,521,422 and any patent issuing on Application Serial No. 732,985.

(Emphasis added.)

Consideration of the amendment filed April 23, 1986, resulted in the issuance of a Notice of Allowance and Issue Fee Due on June 26, 1986. Following timely payment of the issue fee, the patent was granted on December 2, 1986.

The face of U.S. Patent 4,626,538 contains the following notice:[1]

> A portion of the term of this patent subsequent to June 3, 2002 has been disclaimed.

---

[1] It was standard PTO practice in 1986 to identify a specific date in the terminal disclaimer data field on the face of the patent grant. This practice was followed regardless of the form or specific words used in the terminal disclaimer filed under 35 U.S.C. § 253.

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As noted in the remarks section of the amendment filed April 23, 1986, the date corresponds to the then perceived expiration date of U.S. Patent No. 4,521,422, and is the date contained in the terminal disclaimer filed April 23, 1986.

II. Uruguay Round Agreement Act

The Uruguay Round Agreement Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994) (URAA), was enacted on December 8,1994. Among the changes introduced by the URAA were those directed to the term of a patent in the United States. Section 532 of the URAA (Exhibit G) introduced a 20-year patent term. The purpose of the patent term provisions of the URAA was to harmonize the term provision of United States patent law with that of our trading partners which grant a patent term of 20 years from the date of filing of a patent application. Merck v. Kessler, 80 F.3d 1543, 1547, 38 USPQ2d 1347, 1349 (Fed. Cir. 1996).

The patent term provisions adopted in the URAA affect not only the term of patents issued on applications filed after the effective date of enactment of the term provisions (June 8, 1995), but also affect certain patents which were issued and in force on the date of enactment, and patents issued on those pending applications which were filed prior to June 8, 1995. Patents in force on June 8, 1995, are entitled under the patent term resetting provisions of 35 U.S.C. § 154(c)(1) to the longer of the 17-year term from grant of the patent or a 20-year from filing term, subject to any terminal disclaimers.

The Administration and Congress provided explicit guidance on how the term of a patent in force subject to a terminal disclaimer would be affected by the patent term resetting provisions of the URAA. Specifically, Congress approved a Statement of Administrative Action (Exhibit H) that was proposed to implement the agreements that

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were submitted to the Congress on September 27, 1994.[2] As noted at the beginning of the Statement of Administrative Action:

> . . . this Statement represents an authoritative expression by the Administration concerning its views regarding the interpretation and application of the Uruguay Round agreements, both for the purposes of U.S. international obligations and domestic law. Furthermore, the Administration understands that it is the expectation of the Congress that future Administrations will observe and apply the interpretations and commitments set out in this Statement. Moreover, since this Statement will be approved by the Congress at the time it implements the Uruguay Round agreements, the interpretations of those agreements included in this Statement carry particular authority.

1994 U.S.C.C.A.N. 4040.

The portion of the Statement of Administrative Action relevant to the patent term resetting provisions of § 154(c)(1) provides as follows:

> . . . . section 532(a) of the implementing bill amends section 154 to provide that the term of a patent in force on, or that results from an application filed before, the date that is six months after the date of enactment of the Uruguay Round Agreement Act will be the greater of 17 years from the date of patent grant or 20 years from the date of filing of the application leading to the patent. A patent whose term has been disclaimed under section 253 of Title 35 due to another patent on an invention that is not patentably distinct from but was owned by or subject to an obligation of assignment to the same person shall expire on the date of the other patent. A patent whose term has been disclaimed under section 253 of Title 35 independent of another patent shall be reduced by the length of the originally disclaimed period.

1994 U.S.C.C.A.N. 4296 (emphasis added).

It is clear that the Administrative Action Statement addresses two situations where a terminal disclaimer would affect the term of a patent in force. First, where the terminal

---

[2] URAA, Section 101(a)(2) of Title 1, Subtitle A, 108 Stat. 4814 (Exhibit I).

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disclaimer was filed to overcome a double patenting rejection, the Administrative Action Statement clearly indicates that the effect of the patent term resetting provisions of § 154(c)(1) is that the patent containing the terminal disclaimer "shall expire on the date of the other patent." In the second situation, the terminal disclaimer has been filed independent of another patent, such as a terminal disclaimer filed in conjunction with a petition to revive an abandoned application under 37 C.F.R. § 1.137. In that case, the term of the patent is still extended, but the length of the extension is "reduced by the length of the originally disclaimed period."

The patent term resetting provisions of § 154(c)(1) occurred by operation of law. They did not require the adoption of implementing regulations by the Commissioner or any action on the part of affected patentees or patent applicants. This request for a certificate of correction addresses the impact of the URAA on the patent term of U.S. Patent No. 4,626,538.

III. Action Requested

The Commissioner is requested to issue a certificate of correction under 35 U.S.C. § 254 to indicate on the face of the patent that the portion of the term of this patent subsequent to the expiration date of U.S. Patent No. 4,521,422 has been disclaimed.

The patent owner recognizes that the terminal disclaimer as filed disclaimed the term of the '538 patent beyond the expiration date of the '422 patent which was considered to be June 3, 2002 - 17 years from the date of grant. Arguably, the '538 patent was correct as issued, but now contains an error by virtue of the operation of the patent term resetting provisions of the URAA contained in § 154(c)(1). In the event the Commissioner considers the issuance of a certificate of correction under § 254 is not the

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appropriate remedial procedure in these circumstances, relief is requested under 37 C.F.R. § 1.182.

The term of each patent issued by the PTO is important. The term of U.S. Patent No. 4,626,538 is particularly important since this patent claims a product that is currently undergoing premarket regulatory review at the Food and Drug Administration (FDA). This patent is a likely candidate for patent term extension under 35 U.S.C. § 156 once the product is approved by the FDA. The original expiration date of U.S. Patent No. 4,626,538 will have a significant impact on the expiration date of the patent term as extended under 35 U.S.C. § 156.

IV. Arguments

United States Patent No. 4,521,422 was issued on June 4, 1985 for a term of 17 years. Accordingly, the anticipated expiration date of the '422 patent at the time of grant was June 3, 2002. All maintenance fees have been paid on the '422 patent.

During the prosecution of the application that matured into U.S. Patent No. 4,626,538, applicants filed a terminal disclaimer to overcome a double patenting rejection based on the '422 patent. A terminal disclaimer was filed under 35 U.S.C. § 253 and 37 C.F.R. § 1.321(b). It is clear from the terminal disclaimer itself that the disclaimer was considered to be linked to the then perceived expiration date of the '422 patent by the specific recitation of the perceived expiration date of the '422 patent (June 3, 2002), and by the averment that any patent granted on the subject application would be enforceable only for and during such period that the legal title to the patents, including the '422 patent, shall be the same. The prosecution history of the '538 patent expressly states that the terminal disclaimer was submitted to disclaim the term of the patent "which would extend

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beyond the expiration date of U.S. Patent No. 4,521,422 (June 3, 2002)," along with the averment regarding common ownership (page 2 of amendment filed April 23, 1986). The '538 patent as granted on December 2, 1986, contained the notice that "The portion of the term of this patent subsequent to June 3, 2002 has been disclaimed." All maintenance fees have been paid on the '538 patent.

Under the URAA, the patent term of the '422 patent was reset to expire 20 years from the date of the original filing - i.e. June 23, 2003. The '422 patent issued on an application that was a continuation-in-part of an application filed June 23, 1983. The '422 patent was a patent in force on June 8, 1995, and thus entitled to the provisions of § 154(c)(1).

Similarly, the '538 patent is entitled to the patent term resetting provisions of § 154(c)(1) because it was a patent in force on June 8, 1995. As noted above, the patent term resetting provisions of § 154(c)(1) are subject to any terminal disclaimers. The Administrative Action Statement accompanying the URAA makes clear that when a patent has been terminally disclaimed to overcome a double patenting rejection over a first patent, the patent term resetting provisions of § 154(c)(1) by operation of law result in the extension of patent term of the disclaimed patent to the date of expiration of the first patent. The consequences described in the Administrative Action Statement are clear, mandatory ("shall expire"), and are not linked to any form or wording contained in the terminal disclaimer. Accordingly, it is respectfully submitted that the patent term resetting provisions of § 154(c)(1) result, by operation of law, in resetting the expiration date of the '538 patent to the reset expiration date of the '422 patent - i.e. June 23, 2003.

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It is clear from the terminal disclaimer and prosecution history of the '538 patent that the terminal disclaimer was filed under 35 U.S.C. § 253 to overcome a double patenting rejection. It is equally clear that the '538 patent was a patent in force on June 8, 1995, and thus entitled to the benefits of the patent term resetting provisions of § 154(c)(1). The face of the '538 patent now contains an error which can be corrected by Certificate of Correction under § 254. An appropriate Certificate of Correction is attached (Exhibit J).

We are aware that the PTO has addressed the issue of the effect of § 154(c)(1) on patents containing a terminal disclaimer. See e.g., decisions rendered in U.S. Patent Nos. 4,346,116 (Exhibit K) and 4,654,073 (Exhibit L). It is not apparent in either of these decisions whether the PTO considered the effect of the authoritative expression of Administration and Congressional intent contained in the Statement of Administrative Action. We think there is a compelling argument for correction in this case based on the Statement of Administrative Action.

Even if the Statement of Administrative Action was considered in the prior decisions, correction in this case is consistent with past PTO action on this issue. Specifically, the file history, including the terminal disclaimer, in U.S. Patent No. 4,654,073 indicated that the terminal part of the patent was being disclaimed "beyond the expiration date of United States Patent No. 4,422,864 (expiration date December 27, 2000)." The term of the '864 patent was reset to expire on May 20, 2002, by operation of § 154(c)(1). The PTO issued a Certificate of Correction under 35 U.S.C. § 254 to resolve an alleged ambiguity that was present in the terminal disclaimer that allegedly made reference to two

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(2) dates: December 27, 2000 (the original expiration date), and May 20, 2002 (the reset expiration date).

The '538 file history similarly makes reference, as noted above, to filing a terminal disclaimer to disclaim the term of any patent which would extend beyond "the expiration date of U.S. Patent No. 4,521,422 (June 3, 2002)." (Exhibit F) The expiration date of the '422 Patent as reset by operation of § 154(c)(1) is June 23, 2003. Since the file history of the '538 patent raises the same alleged ambiguity as the file history of the '864 patent, a Certificate of Correction should be issued in the '538 patent.

In the PTO decision involving U.S. Patent No. 4,346,116, a request to rescind the terminal disclaimer under 37 C.F.R. § 1.182 was denied. The request and file history in the '538 patent are dissimilar in several respects from those in the '116 patent. First, no request is being made in the '538 patent to rescind a terminal disclaimer. Second, the file history in the '538 patent makes clear that the terminal disclaimer is linked to the "expiration date of U.S. Patent No. 4,521,422," whereas the file history in the '116 patent does not contain such an explicit statement. Thus, the decision in the '116 patent is not controlling in the circumstances in the present case.

In addition, the arguments relied on by the PTO to support the decision in the '116 patent are not applicable to the facts in this case. For example, the decision in In re Jentoft, 392 F.2d 633, 639, n.6, 157 USPQ 363, 368, n.6 (CCPA 1968), which characterized the filing of an unnecessary terminal disclaimer as "an unhappy circumstance," is not applicable to the facts in this case since the patentee is not alleging that a terminal disclaimer was unnecessary. On the contrary, the issue presented in this case is the impact of § 154(c)(1) on a patent that contains a terminal disclaimer.

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In its decision in the '116 patent, the PTO also relied on a public policy against restoring to the patentee something that has been freely dedicated to the public. This policy as allegedly supported by Altoona Publix Theatres v. American Tri-Ergon Corp., 294 U.S. 477, 24 USPQ 308 (1935). This decision is not, however, applicable to the facts in this case where rights accrue to the patentee by operation of law. Just as the PTO has granted extensions of the patent term under § 156 in patents that contain a terminal disclaimer, so too should patents containing a terminal disclaimer be entitled to the patent term resetting provisions of § 154(c)(1). Finally, there are no diligence requirements in the statute or regulations that would permit the Commissioner to raise an issue about the timeliness of filing a request for a Certificate of Correction under § 254.

For all the reasons advanced above, the patent term of U.S. Patent No. 4,626,538 was reset to expire on the reset expiration date of U.S. Patent No. 4,521,422. To deny the '538 patent the benefits of § 154(c)(1) because of the specific language used in the terminal disclaimer would be to exalt form over substance, and would be clearly contrary to explicit Administration and Congressional guidance contained in the Statement of Administrative Action. Further, when Congress intended that a patent subject to a terminal disclaimer not be entitled to a benefit introduced by the URAA, it specifically so provided. See § 154(b)(2).

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V. Conclusion

The patent term of U.S. Patent No. 4,626,538 was reset according to the provisions of § 154(c)(1) on June 8, 1995, to expire on the reset expiration date of U.S. Patent No. 4,521,422 (June 23, 2003). The patent owner requests that a Certificate of Correction be issued to correct this error on the face of the '538 patent.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Dated: June 15, 1999

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In re Patent No: 4,626,538 :
Application No. 06/732,986 :
Filed: May 13, 1985 : DECISION GRANTING PETITION
Issue date: December 2, 1986 :
Inventor: John P. Rusza et al. :

This is a decision on the communication filed June 15, 1999, which is being treated as a petition under 37 CFR 1.182 to obviate the adverse effects (as noted below) of the recorded terminal disclaimer filed April 23, 1986, and further, that the proffered Certificate of Correction (PTO mistake) be issued to that effect.

The petition is granted to the extent indicated below.

Petitioner correctly notes that due to the patent term resetting provisions of 35 U.S.C. § 154(c)(1) contained in Public Law 103-465, § 532, 108 Stat. 4809 (1994), the expiration date of U.S. Patent No. 4,521,422 (and thus, the instant patent whose term is linked to the term of the '422 patent by way of the aforementioned terminal disclaimer) is not seventeen years from issue, or June 3, 2002; rather, it is June 23, 2003, which, as twenty years from the earliest claimed filing date under 35 USC 120, gives the longer of the two possible terms. As such, the expiration date specified in the terminal disclaimer field of the instant patent, as issued, is now incorrect, and warrants issuance of a Certificate of Correction to that effect. However, in light of possible future changes to the patent statutes, as well as current printing instructions for terminal disclaimers, a date specific in the terminal disclaimer field will not be set forth, nor will the proffered Certificate of Correction be employed.

The instant file is being forwarded to Certificates of Correction Branch for issuance of a Certificate of Correction to indicate that, in lieu of the former statement pertaining to the expiration of the term by way of a terminal disclaimer :

--[*] Notice: This patent is subject to a terminal disclaimer.--

Telephone inquiries relative to this decision should be directed to the undersigned at (703) 305-1820.

Brian Hearn
Special Projects Examiner
Office of Petitions
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

United States Patent [19]

Dusza et al.

[11] **Patent Number: 4,626,538**

[45] **Date of Patent: * Dec. 2, 1986**

[54] **[7-(3-DISUBSTITUTED AMINO)PHENYL]PYRAZOLO[1,5-A]PYRIMIDINES**

[75] Inventors: **John P. Dusza, Nanuet, N.Y.; Andrew S. Tomcufcik, Old Tappan, N.J.; Jay D. Albright, Nanuet, N.Y.**

[73] Assignee: **American Cyanamid Company, Stamford, Conn.**

[*] Notice: **The portion of the term of this patent subsequent to Jun. 3, 2002 has been disclaimed.**

[21] Appl. No.: **732,986**

[22] Filed: **May 13, 1985**

Related U.S. Application Data

[63] **Continuation-in-part of Ser. No. 612,812, May 24, 1984, Pat. No. 4,521,422, which is a continuation-in-part of Ser. No. 506,966, Jun. 23, 1983, abandoned.**

[51] **Int. Cl.[4] A61K 31/505; C07D 471/04**

[52] **U.S. Cl. 514/258; 514/906; 544/281**

[58] **Field of Search 544/281; 514/258**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,178,449	12/1979	Dusza et al.	544/281
4,236,005	11/1980	Dusza et al.	544/281
4,281,000	7/1981	Dusza et al.	544/281
4,521,422	6/1985	Dusza et al.	544/281
4,576,943	3/1986	Tomcufcik et al.	544/281

Primary Examiner—Donald G. Daus
Assistant Examiner—Stephen M. Kapner
Attorney, Agent, or Firm—Susan H. Rauch

[57] **ABSTRACT**

Novel [7-(3-disubstituted amino)phenyl]pyrazolo[1,5-a]pyrimidines useful as anxiolytic, antiepileptic and sedative-hypnotic agents as well as skeletal muscle relaxants, methods of using these compounds, compositions of matter containing them and processes for their production.

15 Claims, No Drawings

Exhibit V

Brief Outline of Applicant's Activities During Regulatory Periods

`SONATA® (zaleplon) CAPSULES
REGULATORY CHRONOLOGY
Testing Phase: IND Submission to NDA Submission
IND No. 36,751

Date	Sent To	Subject
4/16/91	FDA	Initial IND Submission
4/24/91	American Cyanamid	FDA Acknowledges Receipt of IND Application Submission Dated 4/16/91
6/14/91	FDA	FDA Approval of our 5/13/91 Protocol and Comments and Requests Concerning Chemistry
10/22/91	FDA	Protocol Amendment - New Protocol 79-500 and Amendment 1
12/2/91	FDA	Response to FDA Request (June 14, 1991) regarding Chemistry
3/16/92	FDA	Protocol Amendment - New Protocol
5/12/92	FDA	Information Amendment - Pharmacology/Toxicology
6/14/91	FDA	FDA Approval of our 5/13/91 Protocol and Comments Concerning Chemistry
7/9/92		FDA Teleconference Regarding Toxicology
7/20/92	FDA	General Correspondence - Minutes of the Teleconference of 7/9/92 regarding toxicology
9/22/92	FDA	Information Amendment - Clinical (Draft Protocol D79 P7)
11/4/92	Lederle	FDA Comments and Recommendations Concerning Amendment Dated

Date	Sent To	Subject
1/14/93	FDA	Protocol Amendment - New Protocol 79-P7
2/23/93	FDA	Information Amendment - Clinical (Revised Investigator's Brochure); Protocol Amendment - Change in Protocol 79-7 (Amendment 1)
7/9/93	FDA	Information Amendment - Pharmacology/Toxicology
8/2/93	FDA	Protocol Amendment - New Protocol 79-9
7/30/93	FDA	Protocol Amendment - New Protocol (D79 P12)
9/2/93	FDA	General Correspondence - Request for Meeting (End-of-Phase II)
9/28/93	FDA	Protocol Amendment - New Protocol (D79 P12) & Information Amendment – Chemistry
11/3/93		FDA Teleconference Regarding Pharmacology and Toxicology Studies
11/5/93		FDA Teleconference Regarding Chemistry Issues
11/10/93	FDA	Information Amendment - Pharmacology/Toxicology
12/3/93	FDA	Response to FDA Request Per Telephone Conversation of 11/5/93
12/14/93		End of Phase II Meeting
12/20/93	FDA	Information Amendment - Pharmacology/Toxicology
12/21/93	FDA	Response to FDA Request for Information Per Telephone Call of 11/3/93 (Pharmacology/Toxicology)

Date	Sent To	Subject
1/11/94		FDA Teleconference Regarding Dose Selection for Mouse Carcinogenicity Study
1/14/94	FDA	General Correspondence – Minutes From End-of-Phase 2 Meeting
1/28/94	FDA	FDA Response to a Chemistry Amendment Submitted to FDA on 12/2/91
2/7/94	Lederle	FDA Questions Regarding Preclinical Data Submitted 9/28/93 (Mass Balance Study, ^{13}C and ^{14}C)
2/10/94	FDA	Protocol Amendment - New Protocol D79 P509, Information Amendment – Chemistry
2/25/94	FDA	General Correspondence – Minutes of Teleconference on 1/11/94
3/13/94	FDA	Summary of Metabolism Data
3/31/94	FDA	Protocol Amendment - New Protocol D79 P16
5/11/94	FDA	Protocol Amendment - New Protocol 79-18
5/13/94	FDA	Information Amendment – Chemistry
5/19/94	FDA	Information Amendment – Clinical
5/20/94	FDA	Information Amendment – Pharmacology/Toxicology Response to Preclinical Questions From End-of-Phase 2 Meeting (12/14/93)
5/25/94	FDA	General Correspondence – Pharmacology/Toxicology

Date	Sent To	Subject
6/2/94	FDA	Protocol Amendment 79-16
6/8/94	FDA	Protocol Amendment - New Protocols 79-14 & 79-17
6/16/94	FDA	Protocol Amendment - New Protocol 79-507
6/27/94	FDA	Request to Discuss an Additional Phase 3 Clinical Study
6/29/94	FDA	General Correspondence – Request for FDA Meeting on Pharmacology/Toxicology
6/30/94		FDA Teleconference Regarding Status of Mouse Carcinogenicity Study
7/19/94	FDA	General Correspondence – Minutes of June 30, 1994 teleconference
8/1/94	FDA	Protocol Amendment - New Protocol No. 079 P21
8/5/94	FDA	General Correspondence – Meeting Request
8/5/94	Lederle	Reply to June 27, 1994 Letter for Large Phase 3 Trial.
8/8/94	FDA	Protocol Amendment - New Protocol No. 79-19
8/12/94	FDA	Information Amendment – Chemistry
9/15/94	FDA	Protocol Amendment - New Protocol (No. 79-15)
9/30/94	FDA	Response to FDA Requests of 1/28/94 & 2/7/94
10/31/94	FDA	Protocol Amendment - New Protocol (No. 79-508)
11/14/94	FDA	General Correspondence – Request for Statistical Meeting

Date	Sent To	Subject
12/6/94	FDA	Protocol Amendment - New Protocol (No. D79 P22)
12/7/94	FDA	Information Amendment – Chemistry
12/13/94	FDA	General Correspondence – Request for Feedback on Toxicology
6/16/95	FDA	Information Amendment – Pharmacology/Toxicology
9/15/95	FDA	Response to FDA Request: Transfer of IND Sponsorship to Wyeth-Ayerst
9/19/95	FDA	Protocol Amendment - New Protocols (Protocol Nos. 0897A-307-US and CA and 0897A-312-US and CA)
9/20/95	FDA	General Correspondence (NDA Stability Protocol and Design)
9/25/95	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A-114-US)
10/5/95	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A-122-US)
10/6/95	FDA	Phase 3 Meeting Request
10/25/95	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A-127-US)
11/17/95		Phase 3 Meeting
12/5/95	FDA	Information Amendment - Chemistry, Manufacturing and Controls
12/18/95	FDA	General Correspondence - Phase 3 Meeting Summary
12/20/95	FDA	Information Amendment - Pharmacology/Toxicology
1/16/96	FDA	Information Amendment - Chemistry, Manufacturing and Controls

Date	Sent To	Subject
1/17/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-123-US)
2/28/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-141-US)
3/14/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-210-US)
3/15/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-124-US)
4/10/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-208-US)
4/17/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-121-US)
5/14/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-138-US)
5/20/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-140-US)
5/30/96	FDA	Response to FDA request for information regarding toxicology
6/19/96	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-142-US)
6/21/96	FDA	Information Amendment - Pharmacology/Toxicology
8/9/96	FDA	Information Amendment - Chemistry, Manufacturing and Controls
8/29/96	FDA	Protocol Amendment - New Protocol (Protocol No. 08971-143-US)
9/17/96	FDA	General Correspondence - Amended Statistical Analyses for Pivotal Protocols
9/18/96	FDA	Information Amendment - Pharmacology/Toxicology

Date	Sent To	Subject
1/1/97	FDA	Information Amendment - Pharmacology/Toxicology
2/13/97	FDA	Abuse Liability Assessment Document Outline
3/20/97	FDA	Meeting Request: Pre-NDA Meeting
5/7/97		Pre-NDA Meeting
5/27/97	FDA	General Correspondence: Pre-NDA Meeting Summary
6/17/97	FDA	Information Amendment - Pharmacology/Toxicology
6/20/97	FDA	Meeting Request: Phase 3B Plan
6/27/97	FDA	Analyses of Carcinogenicity Studies
7/14/97	FDA	Protocol Amendment - New Protocol (Protocol No. 0897A1-211-US)
8/28/97		Phase 3B Meeting
9/12/97	FDA	General Correspondence - Response to FDA Request Per FAX of July 25, 1997 regarding carcinogenicity data analyses and datasets to be included in the NDA
9/16/97	FDA	General Correspondence - Summary of Phase 3B Meeting
12/30/97	FDA	New Drug Application Submitted to FDA

SONATA® (zaleplon) Capsules
REGULATORY CHRONOLOGY
Approval Phase: NDA Submission to DEA Scheduling
NDA No. 20-859

Date	Contents
12/30/97	Submitted NDA No. 20-859 for Sonata (zaleplon) Capsules and corresponding Abuse Liability Assessment Document.
01/13/98	FDA letter acknowledging receipt of NDA.
01/29/98	FDA letter acknowledging receipt of user fee payment on January 6, 1998.
03/11/98	Letter providing information regarding the eleven well-controlled studies.
05/21/98	Submission providing monitoring information and case report forms for studies 301-US, 306-US, and 307-US/CA.
06/04/98	Letter providing a table indicating years of drug exposure in patients including any comparators.
06/22/98	Submission providing efficacy datasets for studies 209-GE and 210-US (transient insomnia studies).
07/01/98	Submission providing statistical analyses regarding change from baseline for ECG parameters of PR, QRS, QT, and QTc, from studies 101 and 102.
07/01/98	Submission providing efficacy datasets for studies 209-GE and 210-US (transient insomnia studies) in SD2 format.
07/02/98	Submission providing diskettes containing the data sets from carcinogenicity studies.
07/08/98	Submission providing adverse event tables.
07/10/98	Submission providing the DMF cross-reference letter (DMF number 9869).
07/31/98	Submission providing dissolution information.
08/18/98	Submission providing PK/PD modeling information.
09/23/98	Submission providing carcinogenicity data sets for study nos. 419, 450, and 94176.
09/28/98	Submission providing individual PK data from Phase 1 studies.
10/01/98	Submission providing updated stability data from that provided in original NDA.

SONATA® (zaleplon) Capsules
REGULATORY CHRONOLOGY
Approval Phase: NDA Submission to DEA Scheduling
NDA No. 20-859

Date	Contents
10/08/98	FDA chemistry information request letter.
10/22/98	Safety update.
10/28/98	Letter providing a line listing of patients with serious adverse events that correspond to the safety update cut-off of September 30, 1998.
11/13/98	Letter providing narratives for select patients with serious adverse events as a result of the review of the October 28 submission.
11/24/98	Submission providing responses regarding the review of the chemistry section.
11/24/98	Letter providing patient narrative.
01/06/99	FDA Approvable letter
01/06/99	Submission providing a Response to Approvable Letter - Intent to Amend.
02/17/99	Submission providing responses to the review of the chemistry section.
02/26/99	Submission providing a Complete Response to the Approvable Letter.
03/18/99	Submission providing a request for a "Written Request" for FDAMA pediatric exclusivity.
04/09/99	Submission providing draft sample bottle and carton labeling to be used in the initial launch of Sonata.
05/06/99	FDA Fax - revised draft labeling, including request for sleep stage data.
05/18/99	Submission and Fax containing revised draft labeling.
05/28/99	Fax regarding revised draft labeling-Mutagenesis section, specifically endoreduplication in human lymphocyte assay. Also provided were letters from consultants (information was requested during FDA teleconference on 5/28).

SONATA® (zaleplon) Capsules
REGULATORY CHRONOLOGY
Approval Phase: NDA Submission to DEA Scheduling
NDA No. 20-859

Date	Contents
06/10/99	Submission providing additional information regarding the Effects of Sleep Stages section of the labeling.
06/14/99	FDA Fax regarding review of Mutagenesis section of the 5/28/99 fax.
06/30/99	FDA letter providing comments and requesting CMC information.
07/06/99	FDA Fax - revised draft labeling.
07/07/99	FDA Fax requesting capsule samples.
07/08/99	Submission providing responses regarding the review of the chemistry section.
07/12/99	Submission providing Sonata 5 and 10 mg gelatin capsules (shells).
07/13/99	Letter providing corrected chemistry dissolution specifications to a 07/08 submission.
07/22/99	Submission providing a briefing package for the August 4 meeting with the FDA to discuss labeling issues.
07/23/99	Teleconference with FDA to discuss chemistry issues (specifically bracketed bottle sizes).
07/29/99	Submission providing comparative information on bottle sizes as a result of the 07/23 teleconference with the FDA.
08/04/99	Meeting with FDA to discuss labeling
08/05/99	Submission providing revised package insert as a result of the August 4 meeting.
08/06/99	FDA initial request (via telephone) for a Patient Package Insert (PPI).
08/09/99	FDA teleconference to discuss contents and format of PPI.
08/10/99	Submission providing proposed PPI as a result of the August 9 teleconference.

SONATA® (zaleplon) Capsules
REGULATORY CHRONOLOGY
Approval Phase: NDA Submission to DEA Scheduling
NDA No. 20-859

Date	Contents
08/13/99	NDA Approved by FDA
08/13/99	Fax to DEA providing NDA approval letter and approved package insert.
08/16/99	Telephone contact with DEA confirming receipt of faxed approval letter from Wyeth-Ayerst.
09/15/99	Final DEA scheduling of Sonata published in the Federal Register